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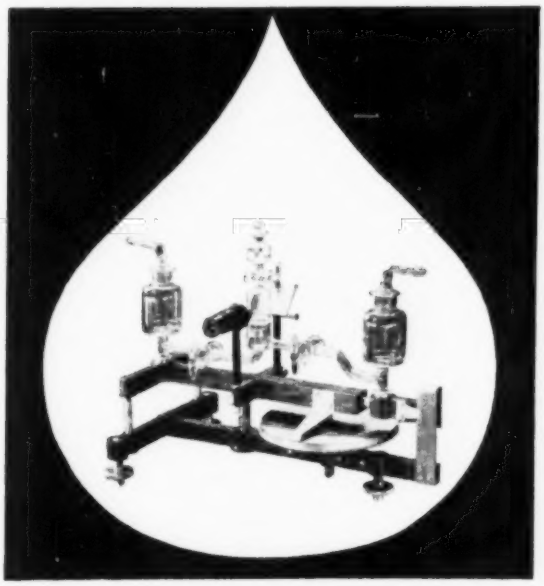

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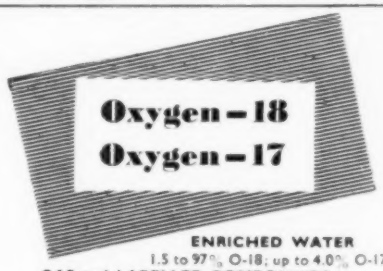

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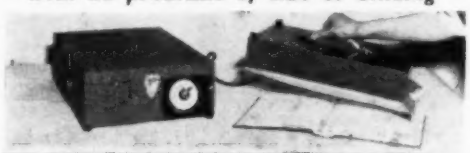

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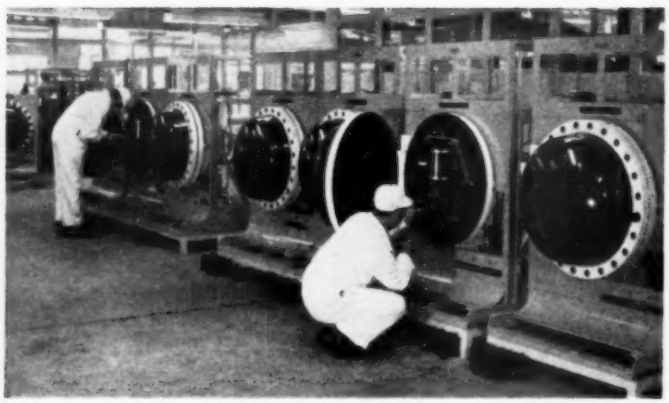

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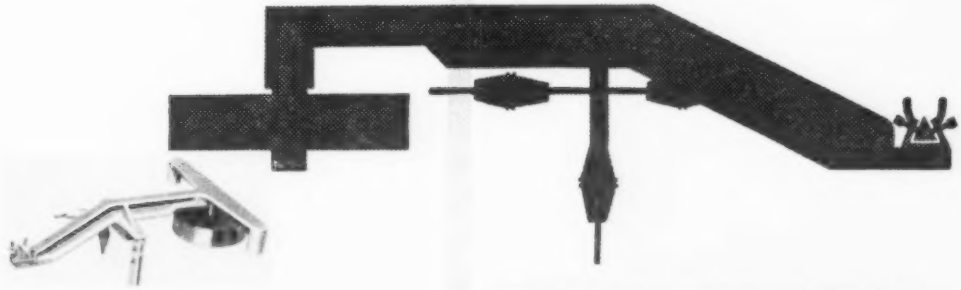

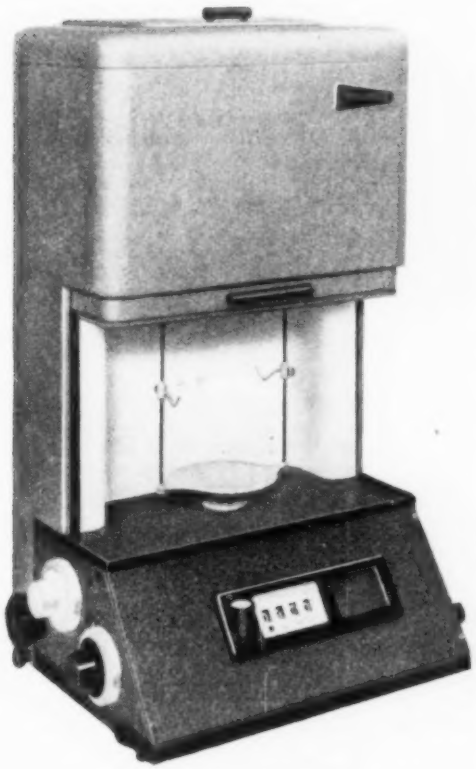

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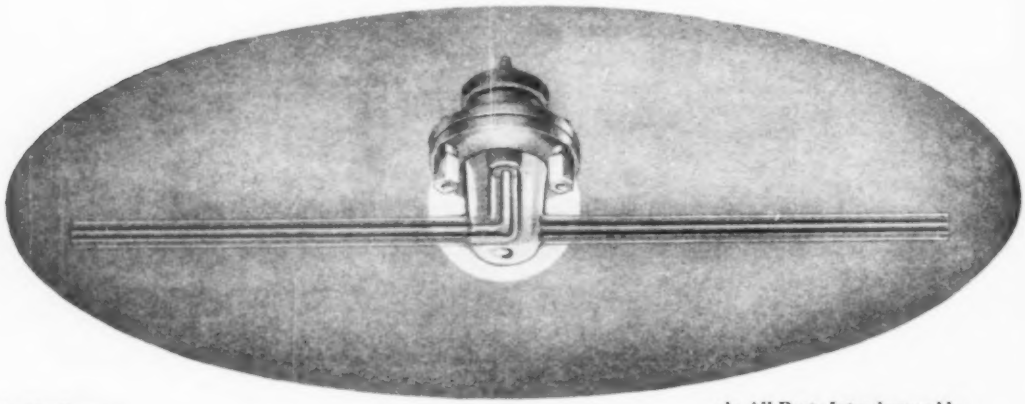

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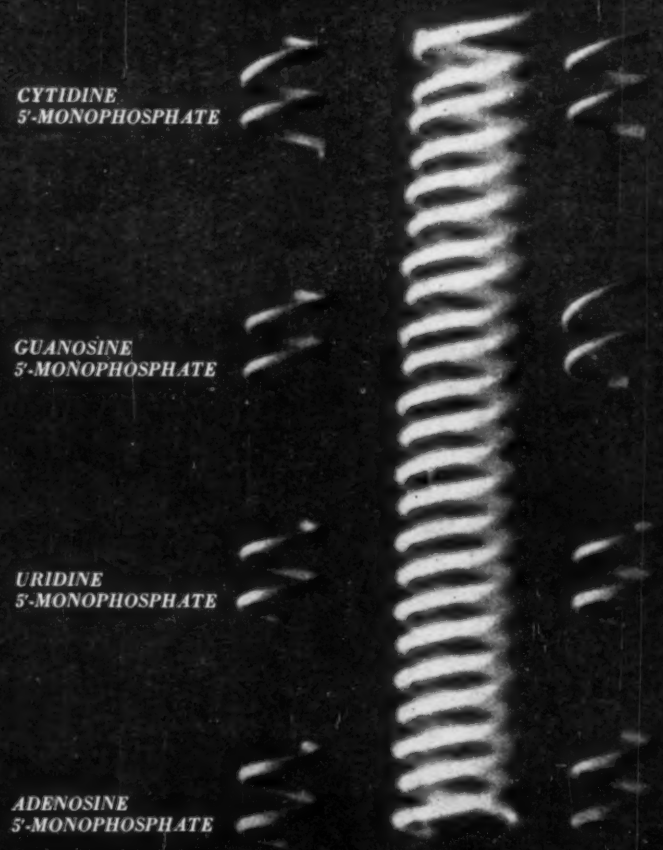

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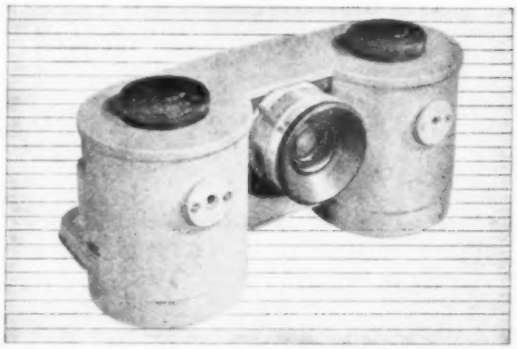

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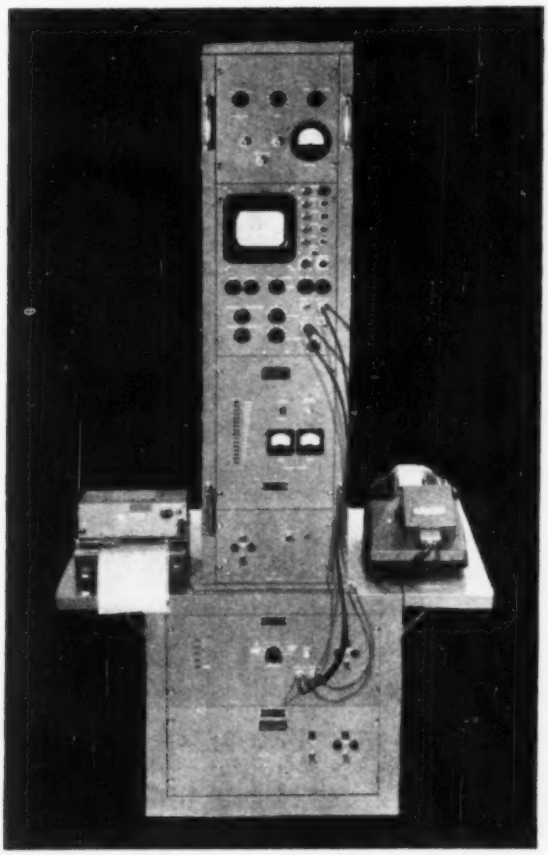

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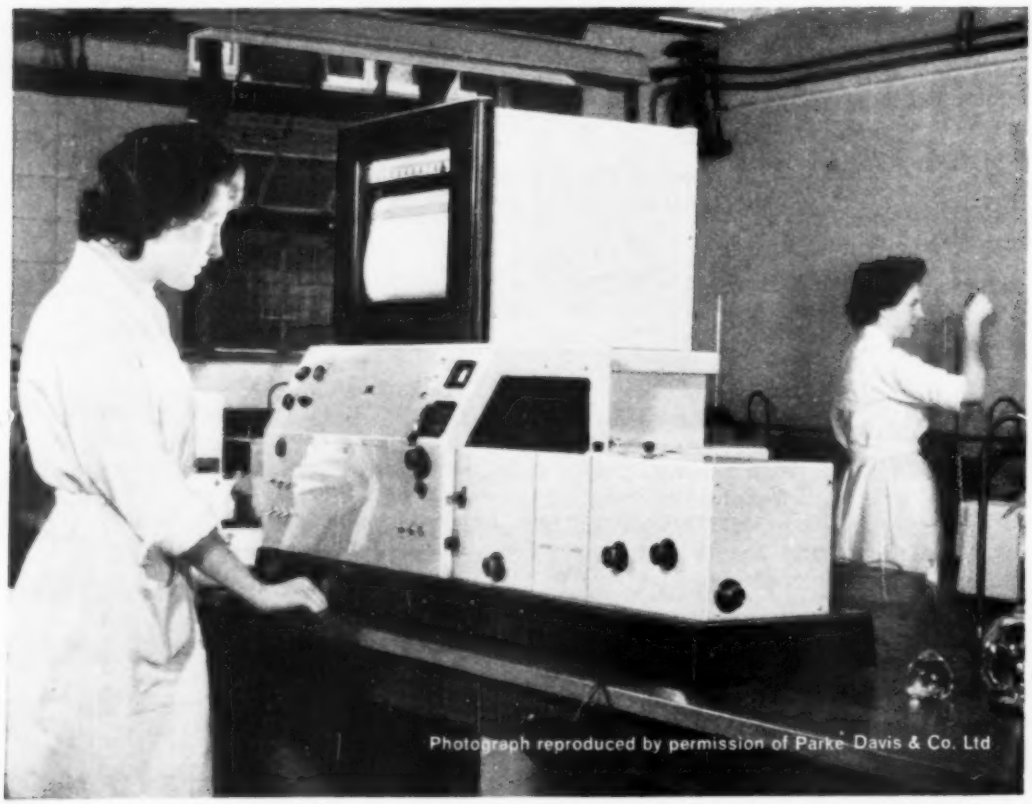

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TAXATION OF SCIENTIFIC BODIES

IN the debate in the House of Lords on November 19, 1960, which arose out of the last report from the Advisory Council on Scientific Policy, Lord Adrian directed attention to the position of scientific societies as affected by the Rating and Valuation Bill now being considered by Parliament. The independent scientific societies in Britain, he pointed out, are a very important part of the organization for fostering progress in both pure and applied science. Their contribution to the encouragement of particular branches of science, as by the work of the Chemical Society or the Geological Society, has been immense, while others, like the Royal Society and the British Association, encourage science in general. They are a main forum for the exchange of ideas, and in retreating during the past decade from the idea of a Science Centre, so stoutly championed by Sir Robert Robinson, the Government has thrown on them a large share of the responsibility for providing scientific and technical libraries service for the country. Even to-day, Government action has scarcely begun to bridge the gap.

Nor is this all. Publication of periodicals as vehicles for original knowledge has become increasingly onerous, partly through the expanding scale of scientific work, and partly through mounting costs of printing, paper and postage. The Nuffield Foundation has already made some tentative inquiries into the possibility of alternative methods of publication and distribution; but, in the meantime, many of the scientific and other learned societies are strained to the utmost in carrying on the task of publication. Nor, as Lord Adrian also noted, should it be forgotten that such societies have also become the representative bodies that can be called on by the State for advice, and membership of which gives status to the individual. In this connexion alone, their value in bringing scientists together is important, and they have even greater direct value in providing incentives and guidance to young men.

Prof. C. F. A. Pantin has directed attention in a letter in *The Times* to another aspect. He emphasizes the extent to which the Government draws on the services of scientific men and women on advisory boards and committees of various kinds in guiding the scientific effort of the nation. For this great service they rarely receive reward of any kind, and their ability to serve efficiently depends directly on the existence of the learned societies which they maintain by their voluntary subscriptions. Their efficiency depends not merely on the maintenance of publication but even more on that personal discourse by which we all keep in touch with rapid advance of knowledge, and which Lord Adrian himself emphasized.

Lord Adrian pointed out that for more than a century the scientific societies of Britain have been assisted by the State in the provision of buildings for some of them, by exemption from rates, and recently by grants for publications. It was a thoroughly British arrangement. The societies have kept their freedom and independence, and the help they receive from the State enables them to shoulder the much greater responsibility that both the rapid advance of science and the national interest demand. There has been no serious complaint about the way the arrangement has been working recently, or about the goodwill of the Government towards scientific societies. It is the danger which threatens their finances through the Rating and Valuation Bill with which Lord Adrian was concerned.

The effect of the proposals of the Bill, in accordance with a recommendation of the Pritchard Committee, would be that societies which are now exempt would in future be required to pay half the full rateable value of their premises. To shoulder these new burdens without any increased help, the scientific societies will be obliged to raise their subscriptions and cut down their expenses; for example, by reducing the size of their periodicals and curtailing the number of meetings they arrange. There may well be room for more careful scrutiny and some reduction in the number of papers published; but it is one matter for that to take place on the initiative of a scientific society itself, and quite another when it is forced on the society by financial stringency alone. No doubt the major national societies will survive the crisis, even if some of them are maimed; but, as Lord Adrian observed, some of the smaller bodies dealing with highly specialized branches of science may be faced with extinction if the recommendations of the Pritchard Report are adopted and there is no countervailing assistance from the State.

When Lord Adrian made this powerful plea for due consideration before action is taken to reduce so seriously the great scientific asset Great Britain has in the independent scientific societies, Lord Hailsham, the Minister for Science, responded by asking if Lord Adrian could induce the societies to inform either him or the Chancellor of the Exchequer on the exact position, which is already under consideration by the Government. Lord Hailsham agreed as to the force of Lord Adrian's remarks, but the Minister of Housing and Local Government, Mr. H. Brooke, made no specific reference to this aspect when moving the second

reading of the Bill in the House of Commons on November 30. He merely explained that the Government had decided to follow the Pritchard Committee's recommendation and repeal the total exemption from rates given by the Scientific Societies Act of 1843 to scientific and other societies, the definition having proved too difficult to apply in practice. Instead, under the Bill, practically every organization now obtaining benefit under the 1843 Act would in future qualify automatically for 50 per cent de-rating, and the local authority would have discretion to give up to complete exemption if it thought fit.

Although it was not mentioned in the debate, a small deputation from the Parliamentary and Scientific Committee had already discussed the matter with the Minister on July 27. Then, after the presentation of the Bill to Parliament, at a meeting of the Rating Sub-Committee, it was agreed to take steps to secure certain amendments during the passage of the Bill through Parliament. First, it was proposed to make it clear that the hereditaments to be given mandatory 50 per cent rating relief under clause 8 (1) will include all hereditaments properly established for scientific purposes as well as charitable purposes. Secondly, it is proposed that the power given to rating authorities in subsection (4) of this clause 8 to reduce or remit the payment of rates chargeable in respect of hereditaments, and including hereditaments not established for profit and concerned with science, should be transferred to the Minister of Housing and Local Government, so that there should be central decision.

On the first amendment, it might be observed that scientists may well feel that there is a certain lack of dignity if relief in this matter is made to depend on charity and not on the nature of the scientific society itself. There may be difficulties, as Lord Hailsham suggested; but the need is a national one and deserves a certain dignity of treatment whether from the point of view of the scientist or of the nation. On the second, because the matter is a national one, it is neither just nor appropriate to place on local authorities the financial obligation to meet charges which properly belong to the whole nation, quite apart from the matter of uniformity in policy which central decision should secure.

When this clause was considered in Standing Committee in the House of Commons on February 14*, the position of the scientific and learned societies was pressed by Mr. D. Wade and Mr. J. T. Price; but the Minister maintained that national importance by itself ought not to be taken as entitling a body to relief from rates. This, of course, specifically rejects the argument advanced by Lord Adrian as well as by Prof. Pantin in spite of the fact that Mr. Brooke himself agreed that it would be a grave loss to the nation if some of the societies in question ceased to exist. There was in fact some general support for the view that since the societies in question are mostly bodies of national character, there is no cogent reason why any special financial assistance they received should come from the local rate-payers. Mr. Mitchison had urged on February 9 that the Government should accept the full re-rating of these societies, and that the consequent burden should be met in full by the Government as a Government concerned with science and the high reputation of the country in these matters.

Because of the form and content of the Bill and the ordinary rules of procedure, amendments requiring the Government to give full rating relief could only be proposed by the Government itself. This undoubtedly appears to be the most dignified procedure; but, while declining to give a pledge that whatever body had received exemption from rates hitherto should now be entitled to turn to the Exchequer for re-imbursement of any rates it might have to pay, Mr. Brooke nevertheless stated that the Treasury would be ready and willing to look at the publication grants which it makes, in particular to the Royal Society, and to consider the position which has arisen. The problem, he said, cannot be solved by legislation; he had been in touch with both the Minister for Science and with the Chancellor of the Exchequer and had their assurance that at the time when the effects on the learned societies could be assessed in the light of the new revaluation they would be fully prepared to meet representatives of the societies for a full examination of those effects on the finances of the societies.

Mr. Brooke maintained that the question is what their financial position will be when the Bill becomes an Act and when the new valuations have been made, and that there will be ample time for these conversations. The societies would not begin to pay rates until April 1964, and then on 10 per cent of their rateable value; but we should know some time in 1962 what the actual liabilities for rates of the societies will be. For this reason, he recommended the Committee not to accept the amendments, but that the Government should be held to the assurance he had given.

During the third reading of the Bill on May 10, Mr. Brooke stated that a deputation from the Royal Society and the British Academy, acting on behalf of the national learned societies, had met the Minister for Science and the Financial Secretary of the Treasury, and that it was generally considered that the needs of such societies should be dealt with outside the framework of the Bill. A joint review of the needs of learned societies of national importance is to be undertaken after the Bill becomes law.

There are thus hopes of a satisfactory settlement which meets the needs of the societies and of the nation on terms conducive to mutual dignity and respect. None the less, there is no justification for any relaxation by scientists over the next few years; they must continue to emphasize the place and function of the scientific society, and its value not simply to the advancement of science but also in the service of the Government and nation.

* Parliamentary Debates: House of Commons—Official Report. Standing Committee D. Rating and Valuation Bill: Ninth Sitting, Tuesday, 14th February, 1961. Columns 409–456. (London: H.M. Stationery Office, 1961.) 9*d*. net.

A SURVEY OF ORIENTAL GRASSES

The Grasses of Burma, Ceylon, India and Pakistan (excluding Bambuseae)

By Dr. N. L. Bor. (International Series of Monographs on Pure and Applied Biology. Division: Botany, Vol. I.) Pp. xviii+767. (London and New York: Pergamon Press, 1960.) 160s. net.

NOTHING gives greater pleasure than to welcome a comprehensive work based on dedicated study by a recognized authority. The author of this book began his work on the Gramineae more than thirty years ago, and it deals with the species, both wild and introduced, of 243 genera of this important family which occur in the sub-continent of India. Presented mainly as a practical handbook, it surpasses the author's modest claims.

The general part of the text gives an excellent account of the morphology of the grass plant (pp. 1–22), deals with dispersal methods, uses of grasses and enumerates certain obnoxious ones. Unfortunately, not all these unusual observations are indexed. The systematic part of the text (pp. 61–681) presents the genera and species grouped in three tribes of Panicoideae and thirty-six of Pooideae. Critics of the alphabetical sequence should read carefully the reasons given on p. 77, and bear in mind the problems implied, as well as exemplified, in the concise, but cogent, section on taxonomy and phylogeny (pp. 61–76). Taxonomists will wish to know the precise date of publication; this was December 14, 1960. The eighty line-blocks, though uneven in style and quality, are of particular interest in showing a comparison of the work of the ten artists. (Not mentioned in the book, they are: Mr. C. Atkinson, Dr. Bor (Figs. 3, 4 and 70), Miss L. Ripley, Miss S. Ross-Craig, Mr. J. Shaw, Miss M. Smith (Figs. 31 and 77), Miss E. M. Stones, Mrs. O. Tate, Mr. P. Taylor and Mr. W. E. Trevithick). The bibliography is good, including almost 600 items; the 89 works by Dr. Bor testify to his preparatory industry. The index lists about 4,800 entities, but omits all varieties. The author acknowledges his indebtedness to J. D. Snowden in the genus *Sorghum*, and Dr. A. Melderis has given assistance in the *Triticeae*.

The magnitude of Dr. Bor's achievement can be gauged from the number of taxonomic entities involved: the 243 genera include 1,250 (± 5) species, but the index shows that he has also placed some 3,500 specific synonyms. Ninety-seven of the genera are monotypic in the area; 60 per cent have less than three species (high proportions, even for Gramineae, perhaps because of introductions); thirty-two have more than ten. The author gives full synonymy for the genera, he has checked all references, examined almost all the type specimens (but does not indicate which) and gives caryological data. The taxonomy is commendably explicit, with full notes covering difficult cases; but one regrets the author's caution, as so few will reach a better position than he to decide some of the issues he leaves "to later research". Need he have deliberately placed the same nine species in both *Erianthus* and *Saccharum*? As to the nomenclature, the author's deep concern with the plants themselves seems to have made him impatient of some of the niceties of the International Code. The inclusion of the same new variety in both *Andropogon polyptychus* and *Dichanthium polyptychus* makes it invalid (*vide* Article 33), like the new combination similarly duplicated on pp. 151 and 212. The text is unmarred by typographical errors, but users may add *Ischnochloa*, *Sorghastrum* and *Themeda* to the list of Andropogoneae on p. 80.

Dr. Bor has completed a study of noble proportions which will become relied on for Asiatic grasses as is Hitchcock's invaluable manual for the North American; the keys make it more useful, the lack of descriptions being less of a handicap for grasses where keys so often use technical characters. Significant scientifically and superlatively well written, the book shows a beautiful balance of original and derived information; at every opening one observes the author's practical knowledge of the grasses of India and his familiarity with the academic sources. This fitting addition to the literature is especially welcome at the present stage in the development of agriculture in Asia. What a pity the high price will tend to restrict ownership of the book to institutions.

JOHN LEWIS

VIRUSES IN DISEASES OF CHILDREN

Viral Infections of Infancy and Childhood

A Symposium of the Section on Microbiology, The New York Academy of Medicine. Edited by Prof. Harry M. Rose. Pp. xi+244. (New York: Hoeber-Harper, 1960.) 8 dollars.

THIS beautifully produced symposium provides a concise account of recently acquired knowledge and current concepts in its chosen field. The approach is epidemiological, with the accent on laboratory aspects.

The first two chapters summarize recent work on the infectivity of ribonucleic acids extracted from poliovirus (H. E. Alexander) and from virus-infected cells (J. S. Colter)—excellent accounts, though of questionable relevance to many readers of this book. About half the 232 pages of text are devoted to enteroviruses, opening with chapters on coxsackie infections (H. L. Hodes) and virus myocarditis (S. van Creveld). The latter chapter gives a particularly useful review and an account of the outbreak of Coxsackie myocarditis of the newborn in Amsterdam in 1955. This dangerous disease is a threat to infants in the nurseries of maternity units, and van Creveld suggests the possibility of active immunization of pregnant women or gamma-globulin prophylaxis for infants born during epidemics of 'summer grippe'. The general properties of *ECHO* viruses are described by J. L. Melnick, and A. B. Sabin presents a particularly well-arranged review of the role of *ECHO* viruses in human disease. Fever, meningitis, and sometimes skin rash have been prominent features of various outbreaks, but associations with such other symptoms as diarrhoea and respiratory illness also appear to be significant. D. A. J. Tyrrell and his colleagues describe their investigations on the outbreak of meningitis and skin rash in England in 1956, caused by type 9 *ECHO* virus, which resembles a Coxsackie group *A* virus in its virulence for suckling mice. Long-term observations of enterovirus infections among children in a Washington orphanage are summarized by L. Rosen and associates. Dalldorf discusses the increasingly recog-

nized role of enteroviruses other than poliovirus in paralytic disease.

Respiratory infections are introduced with a challenging and controversial exposition of the principles of influenza vaccination by F. M. Davenport and A. V. Hennessy, a subject discussed further by E. C. Curnen. There follows an account by A. Isaacs of interferon, which offers an alternative method of approach to control of virus infections. R. M. Chanock and his associates give a useful review of newly discovered respiratory agents, sounding a proper note of caution in relation to interpretation of associations of these viruses with disease. Adenoviruses are surveyed briefly by W. P. Rowe, who also gives an excellent account of salivary gland virus and related infections of animals. Recent advances in varicella and measles are reviewed by S. L. Katz and his colleagues.

This book will be of particular interest to medical virologists, clinical pathologists and clinicians who are concerned with infectious diseases and children.

N. R. Grist

FACTS ABOUT INDUSTRIAL GROWTH

Patterns of Industrial Growth, 1938–58

(Statistical Office of the United Nations, Department of Economics and Social Affairs.) Pp. viii+472. (New York: United Nations; London: H.M. Stationery Office, 1960.) 8.50 dollars; 60*s*. 6*d*.

THE statistical staff of the United Nations has made a heroic attempt to present a picture of industrial growth during twenty years in the 'free' world. In many of the tables the countries are grouped by continent or sub-continent; still more valuable is a four-fold classification by degree of industrialization. Data are given for 1938, 1948, 1953 and 1958 or for the periods lying between each. There are also separate data presented for each country.

The volume should be of the utmost use for students of economic growth, but it should also be serviceable to those of more general interests, whether political or technological. Many a generalization can now be checked by reference to the facts; it is likely that many misconceptions will be removed.

Some of the most prominent tables show growth expressed as average annual percentage rates of increase in each of the three periods. This gives the right orientation, since the most interesting problems of modern economics are concerned with the interrelations between growth-rates. The most central figure in the volume is that giving the average world figure for the annual rate of growth in mining and manufacturing together, namely 4·4 per cent per annum. The increase in output for each person employed in them was 2·0 per cent per annum or 2·7 per cent per annum—depending on the method of measurement.

The lowest class of countries, by degree of industrialization, showed an increase in production of 4·6 per cent per annum, and, it is satisfactory to note, an increase in output per person of 1·7 or 2·1 per cent. But the growth was from a very low level. The value added per person employed in manufacturing in the lowest class group in 1953 was less than a quarter of the value added for each person so employed in Europe, and little more than a twelfth of that per person employed in the United States and Canada (together).

There is a striking table (p. 17) showing a close correlation between the rate of increase of production and the rate of increase of production for each person engaged. No support at all (pp. 26–9) can be found for the view that strong growth tends *per se* to be inflationary; there is no correlation between the rate of industrial growth and the degree of inflation as between countries.

Much selection was needed even for this massive volume. It could be argued that too much space is given to tables of percentage distribution between groups. The explanatory text is workmanlike and raises many interesting points, but in regard to causes we can still only be at the beginning of judgment.

Roy Harrod

PLANT PATHOLOGY

Plant Disease Handbook

By Dr. Cynthia Westcott. Second Edition. Pp. xii+825. (Princeton, N.J.: D. Van Nostrand Company, Inc.; London: D. Van Nostrand Company, Ltd., 1960.) 101*s*. 6*d*.

THIS is an enlarged edition of the book by the same author written some ten years ago, and except for slight alterations the layout remains the same. This edition, however, deals with a much wider range of host plants, and there is a noticeable expansion in most sections as a result of discoveries in research during the past decade. The book in fact lists more than 2,000 diseases occurring on more than 1,000 host plants.

It is a large book of five chapters preceded by an author's note on "How to use this Book". The first three chapters are very short—Chapter 1 is the usual introduction to the subject describing the nature of plant diseases and the principles underlying their prevention or control. Chapter 2 gives an up-to-date account of the chemicals used in control practices, and Chapter 3 is a list of the various plant pathogens, with special attention paid to the fungi, in the form of a short classification.

The next two chapters occupy nearly 700 pages between them and provide what we can call the substance of the book. Chapter 4 includes no less than 40 different types of disease placed in sections which have been created in somewhat arbitrary fashion according to symptoms shown by the hosts (for example, cankers, galls, leaf spots, mildews, rusts, wilts and so on). These sections are in alphabetical order, and in each, the various pathogens which can cause that type of disease appear in alphabetical order accompanied by details of suitable control measures, and the life-history and structure of the parasite. Chapter 5 is a list of host plants in alphabetical order according to the common name or the Latin name where the author considers this is more helpful in avoiding confusion. Below each host name is a full list of its diseases with short comments about the more important ones. At the end there are a glossary, a selected bibliography and a good index. For the purpose of emphasizing special diseases or important parasites there are about 100 illustrations in the form of photographs or line drawings. The paper and print are of the high quality which we always associate with American publications of this kind.

The book is, in the main, a list of plant diseases, but I think it is more than that. It covers an extensive field, and is a condensation of experience gained by the author over 30 years while travelling about the American continent to give advice on plant disease problems. There is certainly no comparable book in this field in Great Britain. Its scope is vast and its contents are intended for American nurserymen, growers and advisers, but even allowing for plants peculiar to the American continent I consider there is much in its pages which can be of value to horticulturists and plant pathologists in Britain. The diseases of ornamental plants are well catered for, and this branch of pathology is one in which British pathologists are not well versed.

The book claims that without special training, seedsmen and growers will be able to use it as a working guide and reference book in diagnosing and treating plant diseases. I doubt whether such people will appreciate the rather formidable lists of scientific names, and whether laymen in general can achieve accurate diagnoses despite the apparent simplicity of the system here propounded. Nevertheless, I consider that the book can provide valuable assistance to professional horticulturists, advisors and plant pathologists generally. Much of the information has had to be condensed, but it is still an impressive collection of facts skillfully cross-referenced so that most people will find little difficulty in finding quickly the knowledge they seek. It is my opinion that Prof. Whetzel, to whom the book is dedicated and whom I remember with affection, would have been pleased with this contribution by his former pupil.

D. E. Green

CONSTANTS FOR BINARY SYSTEMS

The Physico-chemical Constants of Binary Systems in Concentrated Solutions

By Prof. Jean Timmermans. Vol. 4: Systems with Inorganic + Organic or Inorganic Compounds (Excepting Metallic Derivatives). Pp. xi + 1332. (New York: Interscience Publishers, Inc.; London: Interscience Publishers, Ltd., 1960.) 293s.

THIS volume is the last of a series of four prepared by offset printing and contains 900 pages of data on binary mixtures in which at least one of the components is an inorganic compound. The general arrangement follows that adopted in the earlier books and the same properties are recorded. Volume 4 presents the long-awaited indexes of which there are three, one for organic compounds, one for inorganic compounds and one for authors' names. Binary mixtures are not indexed, but under a molecular formula appears the name of one of the components followed by an unclassified list of all pages where the properties of mixtures containing that compound appear. This is a very unsatisfactory arrangement. Suppose, for example, that it was required to find the densities of acetic acid-benzene mixtures, then 166 pages under the title acetic acid would have to be searched. The author index is simply an alphabetical bibliography, so while it is possible to take a page of the main text and find the source of the work cited, it is not possible to look up an author's name and find where his work is included in these volumes.

A pair of names of compounds printed boldly at the head of each page affords assistance in searching the book, but it is a pity that somebody conversant with the peculiarities of the English language was not consulted regarding these titles so that names such as sulphur anhydride and carbon oxide could have been avoided. Some errors were noted in this volume, which contains four pages of errata applicable to Volumes 1–3. However, most of the errors previously pointed out by myself and other reviewers have not been listed. The book ends rather quaintly with a short list of papers which the author has not been able to find.

In spite of the imperfections of the indexing of these volumes this work will be invaluable to many workers as a first reference.

E. F. G. Herington

PHYSICAL TECHNIQUES IN METALLURGY

The Physical Examination of Metals

Edited by Prof. Bruce Chalmers and Prof. A. G. Quarrell. Second edition. Pp. vii + 917. (London: Edward Arnold (Publishers), Ltd., 1960.) 168s. net.

IN the present edition of this book one large volume replaces the two volumes of the first edition. Further, the original authors have become editors for a team of contributors who provide coverage of what is relatively broad subject-matter. This change, of course, represents a current trend, and although the method has disadvantages, it is well suited to the subject in question. The book is thus a completely new one.

It deals with numerous methods of examination, ranging from those providing information on the atomic scale to those concerned with the detection of flaws. Somewhere in between come techniques for the measurement of basic electrical, thermal, and magnetic properties. Apart from the more obvious topics, the book includes details of many not necessarily expected, such as the damping capacity of metals, measurements of elasticity using mechanical waves, the use of radioactive isotopes, and vacuum techniques. A relevant method not included is that of radiography, but presumably the editors think that this is more than adequately covered in other books. However, in this connexion it should be pointed out that other X-ray techniques, such as X-ray diffraction and microradiography, as well as autoradiography are described.

For each subject the underlying physical principles are well described in clear and satisfactory physical language. The actual experimental methods are discussed, and the treatment is illustrated by typical results. No doubt there are omissions, particularly in detail, and the approach in some sections may place most emphasis on the physics of the subject. However, even if this is true, the book unquestionably achieves its aim, that is to bring together for metallurgists the principles of a wide range of physical techniques.

The volume is attractively produced, well printed and illustrated, and the text is clearly presented. All concerned with its production should derive satisfaction from the final result.

A. R. Bailey

Annual Review of Microbiology

Vol. 14. Edited by Charles E. Clifton, in association with Sidney Raffel and Mortimer P. Starr. Pp. vii+391. (Palo Alto, California: Annual Reviews, Inc., 1960.) 7 dollars.

OVER a period of thirteen years, microbiologists have become confident of finding in the *Annual Review of Microbiology* concise and critical surveys of literature covering a wide range of topics. Volume 14 comes up to the standard set by its predecessors.

This year, out of a total of seventeen articles, four will be of direct interest to virologists. Recent observations relating to the fine structure of virus-infected cells have been ably reviewed by Rose and Morgan, although it is, perhaps, to be regretted that this article is not illustrated. D. L. Walker, discussing *in vitro* cell-virus relationships resulting in death of the cell, provides a valuable survey of the links between cell degeneration and virus-induced metabolic alterations. Intramural spread of bacteria and viruses in human populations is discussed by Williams, and Kissling reviews ecological aspects of arthropod-borne viruses of man and other animals.

Scherbaum's contribution provides an overdue comparison of observations on synchronously dividing micro-organisms with established knowledge of normal cellular metabolism. In discussing the problem of protein synthesis, Novelli has focused his attention on the sequence of enzymic steps between free amino-acids and the formation of peptide bonds, as observed in cell-free systems.

Other topics reviewed include: microbial nutrition; nutrition, metabolism and pathogenicity of mycoplasmas; variation in phytopathogenic fungi; genetics and cytology of *Chlamydomonas*; gene action, a review of the gene-to-protein relationship; immunological speculations; interpretation of immuno-diffusion tests; energy metabolism of chemolithotrophic bacteria; industrial fermentations; intracellular symbiosis in insects and enzyme localization in bacteria.

This volume also includes a cumulative index of authors and chapter titles for Volumes 1–14, an addition which will be of inestimable value to all faced with the task of reviewing the literature.

B. A. Newton

Non-Benzenoid Aromatic Compounds

Edited by David Ginsburg. Pp. xii+543. (New York: Interscience Publishers, Inc.; London: Interscience Publishers, Ltd., 1959.) 135*s*.

THE editor was clearly faced with a dilemma in devising a terse yet fully descriptive title for this collection of review articles. As Sir Robert Robinson points out in the foreword, the word 'aromatic' in its ordinary sense was applied to benzene and its derivatives; later it began to imply a measure of stability associated with a benzenoid structure. This brings in the pyridine group, and there is a remarkable similarity in the physical properties of analogous compounds in the thiophen and the benzene series. At the other end of the scale, it was stated at the Chemical Society Symposia, Bristol, 1958 (Special Publication No. 12) and reiterated herein that cyclo-octatetraene shows no aromatic character and behaves as a typical polyolefin.

Appropriately, therefore, the first chapter discusses 'aromaticity' from the theoretical side for both benzenoid and non-benzenoid compounds, with particular reference to the π-electron concept. The chapter on the cyclobutadiene group, which includes diphenylene, is a considerably extended version of matter presented at Bristol. The chemistry of ferrocene and related compounds forms the major part of the section on cyclopentadiene derivatives: pentalene and heptalene follow. Azulenes were considered at Bristol, but are here discussed in great detail in two chapters dealing respectively with the theoretical and preparative aspects; the latter includes most of the recent work of Hafner. The seven-membered systems, tropones and tropolones, form another major topic, a condensed form of more than five hundred papers; this group includes colchicine. The final two chapters discuss shortly cyclo-octatetraene and higher cyclopolyolefins.

To the main texts of most chapters, notes of later publications have been added at the proof stage, their number indicating the lively interest being taken in these subjects. We thus have a timely, authoritative, well-documented and up-to-date series of monographs on an interesting group of substances.

B. A. Ellis

Investigations on Norwegian Cirque Glaciers

Edited by W. V. Lewis. (Royal Geographical Society Research Series, No. 4.) Pp. iv+104+19 plates. (London: Royal Geographical Society and John Murray (Publishers), Ltd., 1960.) 22*s*. 6*d*.

THIS volume gathers together many valuable observations which are mainly concerned with two small cirque glaciers in the Jotunheim, Norway. These particular glaciers have been studied in great detail by a number of specialists, each of whom reports his or her own observations in the book. The geology of the area, as it affects glacial action, is usefully discussed by Dr. M. H. Battey, while Mrs. J. M. Grove supplies very detailed observations of the ice banding of both glaciers, from which she deduces their régime and movement. A detailed physical analysis of the ice-fabric of Vesl-Skautbreen is contributed by Dr. R. J. Adie, and survey results are briefly discussed by J. E. Jackson and Miss E. Thomas.

The major contribution is the valuable analysis by Dr. J. G. McCall of observations made in two tunnels cut through to the corrie back-wall. These results, which required extremely accurate survey work, have given a detailed picture of the mechanics of flow of a small and fairly simple type of corrie glacier. They show that although rotation is important it is not the only type of movement. The observations made of the ice–rock contact at the base of the glacier are incorporated in a discussion of the processes of corrie formation. W. R. B. Battle's contribution discusses techniques and results of recording changes in temperature in bergschrunds, mainly at the Jungfraujoch, Switzerland, and in Norway, with the view of obtaining quantitative evidence of the part played by thaw-freeze in corrie formation. The first and last chapters are contributed by the editor, W. V. Lewis, in which he introduces the authors and sums up the results by applying them to the formation of a typical Lake District corrie, Blea Water.

Although much of the work reported here was done nearly a decade ago and some results have already been published, this very well-produced and illustrated volume is a worth-while contribution to glaciological literature.

C. A. M. King

THE AMINO-ACID SEQUENCE OF SPERM WHALE MYOGLOBIN

Chemical Studies

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APPLICATION of the method of isomorphous replacement has enabled Kendrew and his colleagues to determine the structural configuration of sperm whale myoglobin first to a resolution of 6 Å. (ref. 1) and more recently to a resolution of 2 Å. (ref. 2) by X-ray analysis of type-*A* crystals of the protein. At the suggestion of Dr. Kendrew, a detailed chemical study of the primary structure of the protein was initiated several years ago, and is being continued by one of us (A. B. E.) at Cambridge. Some of the results obtained thus far in the chemical approach are summarized in the present article. Recently, Kendrew *et al.* (see accompanying article) succeeded in deriving an almost complete amino-acid sequence from the electron density distribution at 2 Å., and the correlation of their proposed sequence with the chemical results is presented in their article.

Our investigation has been concerned with three problems: (1) the derivation of an empirical formula for sperm whale myoglobin; (2) the fission of the single peptide chain in the protein by tryptic hydrolysis as a preliminary step in the elucidation of the amino-acid sequence; and (3) the identification of the tryptic peptides derived from the ends of the peptide chain by end-group methods and sequence determinations.

Amino-acid Composition of Sperm Whale Myoglobin

Since the earlier work of Bodo and Kendrew (personal communication) had demonstrated that crystalline sperm whale myoglobin could be resolved chromatographically into several components, an inquiry into the nature of the structural variations responsible for the inhomogeneity became of considerable importance in connexion with more refined X-ray studies, as well as with the projected, detailed chemical work.

Crystalline sperm whale myoglobin (samples kindly provided by Dr. J. C. Kendrew) was fractionated by the method of Bodo (personal communication; cf. Boardman and Partridge[3]). The protein was chromatographed as the carboxy derivative (COMb) at 4° on the sodium form of 'Amberlite *IRC*-50' at *p*H 5·86 and *p*H 5·88, with citrate buffer, 0·34 *N* in sodium ion concentration, saturated with carbon monoxide, as eluent. Resolution of the protein into five hæm-containing components, and approximately 2 per cent of colourless proteins was achieved. Its chromatographic behaviour in the *p*H range 5·82–5·92 was studied with the view of the definition of optimal conditions for the preparation of each of the components in a purified form.

Fractions containing components I, II, III, IV + V, and V as the predominant (>90 per cent) constituents were isolated. Components I, II and III accounted for 2–3, 7–10 and 20 per cent, respectively, of the hæm-containing protein in crystalline sperm whale myoglobin; components IV and V together accounted for the remainder.

After acid hydrolysis, each of the fractions was subjected to quantitative amino-acid analysis by the procedure of Spackman *et al.*[4]. The results are summarized in Table 1, and clearly show that, within the experimental errors, the amino-acid composition of the hydrolysate of fraction I, which is known to be contaminated by colourless protein(s), exhibits a significantly different composition. The constancy of the amino-acid composition of the acid hydrolysates of fractions II–V indicates that components II–V, and probably component I as well, are separate species of myoglobin molecules, which we propose to designate as myoglobins II–V.

Table 1. SUMMARY OF THE AMINO-ACID ANALYSES OF CHROMATOGRAPHIC COMPONENTS OF MYOGLOBIN

The composition of each component is presented in terms of the molar ratios of the constituent amino-acids

Amino-acid	Molar ratios of amino-acid residues				
	Component I	Component II	Component III	Components IV + V	Component V
Aspartic acid	9·08	8·18	8·07	8·04	7·95
Glutamic acid	17·6	18·8	19·4	18·7	18·8
Glycine	11·0	11·2	11·0	11·1	11·0
Alanine	14·9	16·7	17·1	17·2	16·6
Valine	7·71	7·96	7·83	8·36	8·01
Leucine	15·8	17·9	17·9	18·1	18·2
*Iso*leucine	7·89	9·22	8·98	8·94	9·09
Serine	6·78	6·13	6·27	5·90	5·74
Threonine	5·45	4·87	5·15	5·18	5·03
Methionine	1·87	1·95	1·90	1·97	1·98
Proline	5·19	4·06	4·19	3·90	4·03
Phenylalanine	5·85	6·15	5·98	5·96	6·12
Tyrosine	3·70	2·94	2·94	2·79	2·92
Histidine	10·1	11·9	11·6	11·6	11·8
Lysine	16·7	19·2	18·8	18·9	19·1
Arginine	4·15	4·15	3·93	4·01	4·05
Tryptophan				1·86	
Amide ammonia				(7·2)	(7·4)
Integral No. of residues	145*	151*	151*	153	151*

* The totals do not include values for tryptophan. Since the crystalline myoglobin from which these components were separated had a tryptophan content equivalent to 1·58 residues per mole, it is probable that all the components contain two residues of tryptophan.

Romen[5,6] has recently resolved the structurally similar myoglobin of seals (cf. Scouloudi[7]) into several components by chromatography on *CM*-cellulose. The seal myoglobin components differed electrophoretically (cf. finback whale myoglobin[8]), and it is, therefore, possible that variations in amide content are responsible for the chromatographic inhomogeneity.

Since myoglobin IV and myoglobin V represent the major constituents of crystalline sperm whale myoglobin, the fraction containing these two proteins was selected for structural study. To complete the amino-acid analysis, fraction IV + V from sperm whale myoglobin was subjected to alkaline hydrolysis by the procedure of Drèze[9], and the tryptophan content of the hydrolysate was determined by the starch column method of Moore and Stein[10]. The tryptophan value obtained is given in Table 1, and indicates that myoglobins IV and V both contain two residues of tryptophan per molecule. The amino-acid composition of myoglobins IV and V thus involves 153 residues and approximately 7 amide groups. The molecular weight based on this composition (including the hæm group and the terminal molecule of water) is 17,816.

The chromatographic differences between myoglobins IV and V and the other components remain without explanation. The possibility that the components differ in amide content is at present under investigation.

Peptides obtained on Tryptic Hydrolysis of Myoglobins IV and V

The absence of cystine (cf. Table 1) permitted the direct use of the heat-denatured protein as a starting material for work on the peptides. After the protein was subjected to tryptic hydrolysis at *p*H 8 or at *p*H 9 for 16–20 hr. at 40°, the hydrolysate was separated into a soluble fraction, and an insoluble fraction with which all the hæm was associated. From the soluble fraction 20 peptides and free lysine were isolated in yields of 7–82 per cent by chromatography on 'Amberlite *IRC*-50' and 'Dowex 50-*X*2'. The results obtained on amino-acid analysis of these peptides are summarized in Table 2.

The generally high purity of the peptides revealed by the analyses in Table 2 is noteworthy, and the composition of each peptide is clearly defined by the molar ratios of its constituent amino-acids. The compositions are consistent with the specificity of trypsin, since each peptide, with the exception of the carboxyl terminal peptide, Tryp-16 (which will be considered later), contains at least one residue of lysine or arginine. Peptides Tryp-11, -12 and -19 differ from peptides Tryp-9, -14 and -15 only by the presence of an additional lysine residue. It has therefore been tentatively assumed that free lysine (Tryp-7) was released from each of the three regions of the peptide chain represented by these peptides, although their formation as a consequence of transpeptidation cannot be ruled out on the basis of these results alone. In this connexion a peptide of the composition Arg.(Asp,Ala_2,Ileu,Lys).Lys,Tyr was isolated from a *chymotryptic* hydrolysate of the proteins, and since this peptide contains all the amino-acids of peptide Tryp-11, the presence of the latter in tryptic hydrolysates is probably not attributable to transpeptidation.

It should be noted that Tryp-10, isolated in a yield of only 7 per cent (cf. Table 2), is not derived from a unique, unaccounted portion of the amino-acid sequence, since its inclusion as such would necessitate the assignment of a fifth proline residue to the composition of myoglobins IV and V (cf. Table 1). If peptides Tryp-10, -11, -12 and -19 are excluded, the soluble peptides collectively account for 107 residues, including 16 of the 19 residues of lysine and 3 of the 4 residues of arginine.

When the insoluble fraction was exposed to trypsin a second time, small but significant changes were detected in its composition. However, the com-

Table 2. Amino-acid Composition of Soluble Peptides obtained from Myoglobins IV and V after Degradation with Trypsin

The composition of each peptide is presented in terms of the molar ratios of the constituent amino-acid residues. The peptides were isolated by ion-exchange chromatography on a series of columns of 'Amberlite *IRC*-50' and 'Dowex 50-*X*2'. The values for the principal components in each peptide are in black type. Values less than 0·01 unit are omitted from the table. The values in parentheses are not included in the totals

Amino-acid	Peptide																				Total No. of residues from peptides Tryp 1–21
	Tryp-1	Tryp-2	Tryp-3	Tryp-4	Tryp-5	Tryp-6	Tryp-7	Tryp-8	Tryp-9	Tryp-10	Tryp-11	Tryp-12	Tryp-13	Tryp-14	Tryp-15	Tryp-16	Tryp-17	Tryp-18	Tryp-19	Tryp-20	Tryp-21	
Aspartic acid	—	**0·99**	—	—	—	—	—	—	0·01	0·03	**0·91**	0·08	—	**0·98**	**0·97**	—	—	**1·93**	**0·98**	0·08	**2·86**	8
Glutamic acid	**0·98**	—	—	—	—	—	—	—	**3·03**	0·22	0·13	**3·00**	—	—	**1·00**	**1·96**	**1·98**	**2·00**	**1·04**	**1·99**	**1·16**	14
Glycine	0·01	—	—	0·02	—	—	—	—	**0·95**	0·06	0·17	**1·14**	0·04	0·08	—	**2·04**	0·02	**2·10**	0·20	0·09	**3·04**	8
Alanine	**1·01**	—	0·06	**1·01**	—	—	—	—	**2·99**	**0·98**	**1·94**	**3·05**	—	**2·00**	**1·03**	—	**1·02**	**2·02**	**1·09**	0·07	**2·85**	14
Valine	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	**2·11**	—	—	—	2
Leucine	**2·01**	—	—	—	**0·96**	—	—	—	**1·98**	**1·00**	0·06	**2·05**	**1·02**	—	**1·01**	**1·00**	—	**1·02**	**0·98**	**1·01**	0·12	10
*Iso*leucine	—	—	**1·95**	—	—	—	—	—	—	—	**1·02**	0·06	—	**0·97**	—	—	—	**1·98**	0·04	—	0·04	5
Serine	0·03	—	0·06	0·08	0·12	0·04	—	—	**0·98**	0·13	0·21	**0·98**	0·05	0·10	**0·92**	—	—	0·14	**0·96**	**0·97**	0·36	3
Threonine	—	—	—	**1·01**	—	—	—	—	**1·00**	—	0·04	**0·98**	—	—	—	—	**0·98**	—	—	**0·98**	0·03	4
Methionine	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	**0·96**	1
Proline	—	—	**1·03**	—	—	—	—	—	**1·04**	**0·96**	—	**1·13**	—	—	—	—	**0·89**	—	—	**1·03**	**0·99**	4
Phenylalanine	**1·03**	**1·00**	—	—	**0·98**	**0·95**	—	—	—	—	—	—	—	—	—	—	—	—	—	—	**0·95**	5
Tyrosine	—	—	—	—	—	—	—	**0·88**	—	—	—	—	—	—	—	**0·98**	—	—	—	—	—	1
Histidine	—	—	—	—	—	—	—	—	**2·97**	—	0·10	**2·94**	**1·00**	—	—	—	—	**0·85**	—	**1·00**	**1·11**	10
Lysine	0·02	—	**1·02**	**0·98**	**1·07**	**1·05**	**3·00**	**1·00**	**2·07**	**1·06**	**2·03**	**2·32**	**0·98**	**1·03**	**0·99**	—	**1·00**	0·06	**1·90**	**1·03**	**1·05**	16
Arginine	**0·96**	**1·01**	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	**0·94**	—	—	—	2
Total No. of residues	6	3	4	3	3	2	3	2	17	(4)	(6)	(18)	3	5	6	6	6	15	(7)	8	15	107
Yield in per cent	50	42	15	13	42	82	33	45	35	7	20	10	49	62	33	50	72	9	10	56	17	

position was not markedly affected by additional exposures to the enzyme. After exhaustive treatment with trypsin, the insoluble fraction ('core') was subjected to amino-acid analysis, from the results of which the following overall composition of the fraction was deduced:

Asp_2,Glu_6,Gly_4,Ala_3,Val_4,Leu_7,$Ileu_4$,Ser_3,Thr.Phe. Tyr,Try_2,His_4,Lys_3,Arg.

This composition was not markedly altered when the insoluble fraction was subjected to the action of chymotrypsin.

The combined analytical results obtained from the soluble and insoluble portions of the tryptic hydrolysate indicate that all the amino-acid residues in the protein, with the exception of one histidine and one leucine residue, were identified as constituents of the peptides. Collectively, these peptides contain six additional residues (Asp_2,Glu,Gly,Ala_2) not assigned to the composition of myoglobins IV and V. It is probable that these additional residues are present in sequences accounted for by both the insoluble fraction and one or more soluble peptides.

The haem group apparently does not shield the insoluble fraction from the action of trypsin. The composition of the insoluble fraction from a tryptic hydrolysate of urea-denatured globin prepared from myoglobins IV and V was found to be almost the same as that of the insoluble fraction from myoglobins IV and V.

End-group Analyses

Prior to further fractionation, the homogeneity of the peptide material represented by the insoluble fraction ('core') was investigated by end-group analysis. Both the insoluble fraction, and for comparison, the intact protein were subjected to dinitrophenylation by Levy's method[11]. After acid hydrolysis of the dinitrophenyl (DNP) derivatives, a single amino-terminal residue of valine was detected in each case by a combination of the following methods: identification of DNP-valine by paper chromatography[12]; quantitative determination of the valine liberated from DNP-valine by alkaline hydrolysis[13]; and a subtractive procedure in which each polypeptide was subjected to quantitative amino-acid analysis[14] before and after dinitrophenylation. The presence of one DNP-valine residue in the insoluble fraction indicates that the insoluble fraction contains either one peptide with a valine terminal group, or several peptides, one of which possesses a valine end-group, whereas the others have end-groups that were not detected by the procedure used. In the accompanying paper Kendrew *et al.* have deduced that the 'core' must consist of at least two peptides.

Since peptide Tryp-18 is the only soluble peptide containing valine, it was subjected to sequential degradation by Edman's method[15], and the results were compared with those obtained when the protein was subjected to the same procedure. The amino-acids cyclized off at each step were identified by a subtractive method[16], alone or in combination with paper chromatographic identification[17] of the corresponding phenylthiohydantoins. The sequence valylalanine (Val.Ala) was found at the amino-end of the protein, whereas in peptide Tryp-18 the corresponding sequence was found to be valylglutaminylalanine (Val.Glu-NH_2.Ala). The valine terminal peptide in the insoluble fraction thus represents the amino-terminal region of the protein.

The identities of the amino-terminal residues in peptides Tryp-9 and Tryp-21, and the amino-acid sequences in peptides Tryp-1, Tryp-2, Tryp-4, Tryp-5, Tryp-13, Tryp-14, Tryp-15, Tryp-16 (the carboxyl-terminal peptide in the chain), Tryp-17, and Tryp-20 were established by Edman's method. The sequences found are shown in Table 3.

Table 3

Peptide	Sequence
Tryp-1	Ala.Leu.Glu.Leu.Phe.Arg
Tryp-2	Phe.Asp.Arg
Tryp-4	Ala.Thr.Lys
Tryp-5	Leu.Phe.Lys
Tryp-9	N-terminus: Gly
Tryp-13	His.Leu.Lys
Tryp-14	Asp.Ileu.Ala.Ala.Lys
Tryp-15	Ala.Ser.Glu.Leu.Asp.Lys
Tryp-16	Glu.Leu.Gly.Tyr.Gly.Glu-NH_2
Tryp-17	Thr.Glu.Ala.Glu.Met.Lys
Tryp-20	Ser.His.Pro.Glu.Thr.Leu.Glu.Lys
Tryp-21	N-terminus: His

Glutamine, glycine and tyrosine were the principal products liberated from both Tryp-16 and the globin derived from the intact protein by the action of carboxypeptidase *A*, whereas leucine and glutamic acid, as well as alanine, *iso*leucine, threonine and aspartic acid, were released in smaller quantities from the protein. The quantitative similarity in the pattern of release of the principal products liberated in each case substantiates the conclusion that peptide Tryp-16, the only peptide devoid of lysine and arginine, represents the carboxyl-terminal region of the protein.

Work is now in progress on the peptides liberated by the action of chymotrypsin from myoglobins IV and V in order to obtain the information necessary for the connexion, in sequence, of the tryptic peptides along the polypeptide chain.

This work was initiated at the Rockefeller Institute in the laboratories of Dr. S. Moore and Dr. W. H. Stein, to whom we are indebted for their advice and encouragement. Research at Brookhaven National Laboratory was performed under the auspices of the United States Atomic Energy Commission. The work of one of us (A. B. E.) at Cambridge has been facilitated by grants from the United States Public Health Service for a fellowship and for provision of an amino-acid analyser (grant Nos. *A*-3032 and *A*-3032(S1)). We thank Dr. J. C. Kendrew for his continued support of this research and Mrs. Margaret Ross for her skilled assistance.

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A Partial Determination by X-ray Methods, and its Correlation with Chemical Data

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AN earlier article in *Nature*[1] described the general features of the 2-Å. Fourier synthesis of sperm whale myoglobin, and showed that the molecule consists of a number of segments of right-handed α-helix separated by irregular regions. In that article doubts were expressed about the possibility of identifying side-chains in a Fourier synthesis calculated at 2-Å. resolution, at which neighbouring covalently bonded atoms are generally not separately resolved. Interpretative techniques have now been improved, however, and it has, in fact, proved possible to identify many side-chains with assurance, and in many others to narrow the choice to two or three. To determine completely the amino-acid sequence of a protein by X-ray methods alone, it will clearly be necessary to work at higher resolution than 2-Å., as we intend to do in future studies of myoglobin; but in the meantime it has been possible, by correlating the present X-ray identifications with the preliminary chemical results, described in the preceding article by Edmundson and Hirs, to arrive at a tentative amino-acid sequence which, though it is incomplete and contains ambiguities and no doubt some errors, cannot be very far from the truth.

Methods of Identifying Side-chains

The Fourier synthesis is normally represented as a stack of contoured 'Perspex' sections representing the electron density in a series of parallel planes cut through the molecule. The previous article described another method of representation, more convenient for model-building, in which the main features of the density at a grid of points in the structure are represented by coloured clips attached to vertical steel rods; the structure of the molecule can be outlined by building skeleton-type atomic models between the rods in such a way that they follow the density indicated by the clips. With the help of this technique, it was easy to locate all the helical segments of the molecule, and, with somewhat less assurance, to follow the course of the main chain in non-helical regions where it turns corners. Once the main chain has been correctly inserted, the density corresponding to the side-chains can easily be seen emerging from it at the appropriate intervals. It is now often possible to identify side-chains by building atomic models between the rods so as to follow the density, and checking the results by reference to the more detailed information in the contour map itself. We have also made use of special sections cut through the density distribution at any desired angle and position; these sections are prepared by interpolation from the original density function by means of a computer programme, devised for *Edsac* Mk. II by Dr. Joyce Wheeler.

Methods of identification can be summarized as follows:

(1) Once the course of the main chain has been established, the starting point of each side-chain becomes defined, since the position of Cβ is fixed relative to the main chain.

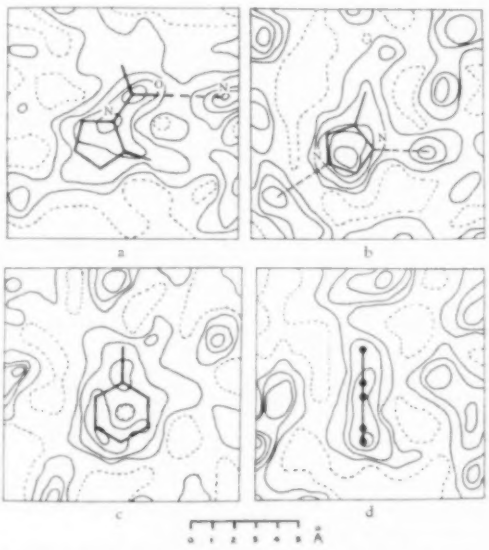

Fig. 1. Sections through parts of the 2-Å. Fourier synthesis showing side-chains. Contour interval 0·5 el./Å.³; atoms not otherwise labelled are carbons. (*a*) Proline, *F*3. The dotted line is a hydrogen bond from the CO group to a NH group along the helix. (*b*) Histidine, *C*1. The dotted lines indicate hydrogen bonds to neighbouring groups, probably ions or water molecules. (*c*) Phenylalanine, *B*14. Note that there is no density peak within Van der Waals distance of the ring atoms. (*d*) Phenylalanine *B*14. Section cut normal to the plane of the ring

(2) Studies of the structures of simpler compounds by X-ray and spectroscopic methods have led to the generalization that, unless strong interactions elsewhere in the molecule impose restraints, the arrangement of the bonds about a singly bonded pair of carbon atoms is always very close to the staggered configuration, the eclipsed configuration being, energetically, relatively unfavourable. A detailed examination of the published structures of amino-acids and peptides (F. H. C. Crick, personal communication) shows that this generalization is applicable to such compounds. We have made the assumption—which our experience here justifies—that, unless there are over-riding reasons to the contrary, the staggering rule is everywhere obeyed within ± 10–15°. It means, for example, that when the Cβ of a side-chain has been correctly placed, only three positions are open to Cγ's, and a search for density can be made in each of these positions in turn.

We have assumed, furthermore, that, in the absence of contrary reasons, such as an interaction with nearby groups, a long side-chain such as lysine is normally in the fully extended (zig-zag) configuration.

(3) Steric considerations are often important in ruling out certain configurations. Thus, in helical

Table 1

1. *X-ray evidence*			2. *Chemical evidence*		
A	1	Val 4	*a*	Val	
	2	Ala 4		Ala	
	3	Gly 5			
	4	Glu 5			
	5	Try 5			
	6	Ser 2, *Ala* 2			
	7	Glu 3, *Ala* 1			
	8	Ileu 4			
	9	Leu 4, *Asp* 1			
	10	Lys 3			
	11	(Not Gly)			
	12	Try 5			
	13	(Not Gly)			
	14	Leu 4			
	15	Leu 4		Core	
	16	Glu 4		4	
AB	1	(Not Gly)			
B	1	Leu 3, *Asp* 1			
	2	Val or *Thr* 5			
	3	Ala 5			
	4	Gly 5			
	5	His 4			
	6	Gly 3, *Ala* 1			
	7	Lys 4			
	8	Leu 3, *Asp* 1			
	9	Thr 3, *Val* 2, *Asp* 1			
	10	Leu 5			
	11	Ileu 5			
	12	Ser 3			
	13	Leu 5			
	14	Phe 5			
	15	*Thr* 3, Lys 2, *Ser* 1			
	16	Ser 3, *Thr* 2		Ser	
C	1	His 5		His	
	2	Pro 4		Pro	
	3	Glu.C 5		Glu.C	20
	4	Thr 4		Thr	
	5	Leu 4		Leu	
	6	*Ser* 2, *Thr* 2	*x*	Glu	
	7	Lys 3		Lys	
CD	1	Phe 5		Phe	
	2	Asp 2		Asp	2
	3	Arg 3	*c*	Arg	
	4	Phe 3		Phe	
	5	Lys 3		Lys	6
	6	His 4		His	
	7	Leu 2, *Asp* 2		Leu	13
	8	Lys 1		Lys	
D	1	Thr 5		Thr	
	2	Glu 4		Glu.C	
	3	Ala 5		Ala	17
	4	Glu 3		Glu.C	
	5	Met 5		Met	
	6	Lys 4		Lys	
	7	Ala 5		Ala	
E	1	Ser 4		Ser	
	2	Glu 2		Glu.C	15
	3	*Asp* 4, Leu 1		Leu	
	4	*Leu* 3, Asp 1		Asp.C	
	5	Lys 3		Lys	
	6	Val, *Thr* or *Ileu* 4		*Val*	
	7	*His* 3, Glu 2		*Glu.N*	
	8	*Gly* 5	*x*	*Ala*	
	9	Ileu 3		*Ileu*	
	10	Glu 2, *Ser* 1, *β-f* 1		*Glu*	
	11	Val or *Thr* 5		*Val*	
	12	Asp 3, *Lys* 1		*Asp*	
	13	*Ser* 3, *Thr* 1, *Ala* 1	*x*	*His*	18
	14	*Ala* 4, Gly 1		*Gly*	
	15	Leu 3		*Leu*	
	16	Gly 5		*Gly*	
	17	Ala 4		*Ala*	
	18	Ileu, *Val* or *Thre* 5		*Ileu*	
	19	Asp 2, *Leu* 2		*Asp*	
	20	Arg 4, *Lys* 1		*Arg*	

1. *X-ray evidence*			2. *Chemical evidence*		
EF	1	Lys 2		*Lys*	
	2	Lys 5		*Lys*	
	3	Gly 2		*Gly*	
	4	Leu or *Asp* 2, *His* 1		*Leu*	
	5	His 5		*His*	
	6	Glu 1, *Ala* 1		*Glu*	
	7	(Not Gly)		*Leu*	
	8	Glu 1		*Glu*	
F	1	Glu or *His* 2		*Glu*	12
	2	Ala 2		*Ala*	
	3	Pro 5		*Pro*	
	4	Thr or *Val* 3, *Ser* 1		*Thr*	
	5	Ala 3, *Gly* 2		*Ala*	
	6	His 2, *Asp* 1		*His*	
	7	Ser 4, *Ala* 1		*Ser*	
	8	His 5	*d*	*His*	
	9	Ala 5		*Ala*	
FG	1	(Not Ala, Gly, *β*-f) Lys?		*Lys*	
	2	(Not Gly)		*Leu*	
	3	Phe 4, *His* 1		*Phe*	5
	4	(Not Ala, Gly, *β*-f) Lys?		*Lys*	
	5	Ileu 2		Ileu	
G	1	Pro 4		Pro	3
	2	Ileu 4		Ileu	
	3	Lys 5		Lys	
	4	Tyr 5			
	5	(Not Ala, Gly, *β*-f)			
	6	Glu 5			
	7	*Phe* 3, His 2			
	8	Leu 3, *Asp* 2			
	9	Ser 4		Core	
	10	(Not Gly, Ala)		*B*	
	11	Ala 4			
	12	Val or *Thr* 4, Ileu 1			
	13	Ileu 3, *Val* or *Thr* 2			
	14	His 2			
	15	Val or *Thr* 5			
	16	Arg, *Leu*, *Asp*, *Lys* 1			
	17	Ala 3, *Asp* 1, *Glu* 1		*Ala*	
	18	*Ala* 3, Thre, *Val*, *Ser* 1		*Thr*	4
	19	Lys 3		*Lys*	
GH	1	His 2		His	
	2	*Ala* 4, *Glu* 1	*x*	Asp	
	3	*Gly* 3, Asp 1		Asp	
	4	Glu 4	*x*	Glu	
	5	Phe 4		Phe	
	6	Gly 5		Gly	
H	1	Ala 5		Ala	
	2	Pro 4		Pro	
	3	Ala 5		Ala	21
	4	Asp 2, *Ser* 2, *β-f* 1		Asp	
	5	Gly 3, *Lys* 1		Gly	
	6	Ala 5		Ala	
	7	Met 5		Met	
	8	Gly 4, *β-f* 1		Gly	
	9	Lys 4		Lys	
	10	Ala 5		Ala	
	11	Leu 5		Leu	
	12	Glu 5		Glu.C	1
	13	Leu 5		Leu	
	14	Phe 5		Phe	
	15	Arg 4		Arg	
	16	Lys 4, *Ser* 1		Lys	
	17	Asp 5		Asp.C	
	18	Ileu 5		Ileu	11
	19	Ala 5	14	Ala	
	20	*Ser* 3, Ala 2		Ala	
	21	Lys 2, *Ileu* 2		Lys	
	22	Tyr 5		Tyr	8
	23	(Not Gly, Ala, *β*-f) Lys?		Lys	
	24	Glu 4		Glu.C	
HC	1	Leu 2, *Lys* 2		Leu	
	2	Gly 5		Gly	
	3	Tyr 5		Tyr	16
	4	Gly 4		Gly	
	5		*b*	Glu.N	

x, discrepancies between X-ray and chemical data. *a*, terminal amino-group. *b*, terminal carboxyl-group. *c*, bonded to propionic acid side-chain of haem group. *d*, Attached to iron atom of haem group.

X-ray data. The degree of confidence in each identification is indicated by a number, with maximum confidence represented by 5. Where a choice of residues is given, that which agrees with the chemical evidence is printed in Roman type, the others in italic type. '*β-f*' means a residue forked at C*β*, that is, Val, Thr or Ileu.

Residues are identified by a letter, or letters, and a number. A single letter refers to one of the helical segments *A*–*H*; a double letter to an irregular region between two helices. A residue is counted as part of a helical segment (*a*) at the amino-end, if its CO group is bonded to NH along the helix, and (*b*) at the carboxyl end, if its C*α* lies between two NH groups bonded to CO groups along the helix.

Chemical data. The numbers in black type are those used by Edmundson to identify tryptic peptides.
Boxes enclose residues the sequence of which has not been chemically determined.
Tryptic peptides believed (on the basis of chymotryptic digestion) to be linked together are so indicated.
Asp.C and Glu.C refer to the acids and Asp.N, Glu.N to the amides.
Peptides the positions of which in the sequence are regarded as doubtful are printed in italics.

The only tryptic peptide isolated by Edmundson and Hirs which is not accounted for in this scheme is **10** (Ala, Leu, Pro) Lys; it is believed on chemical grounds that this residue may be an artefact.

segments, one of the three Cγ positions permitted by the staggering rule is sterically impossible, because an atom in that position would be too close to a carbonyl oxygen atom in the helix. Again, the close-packed internal structure of the molecule means that neighbouring side-chains are generally in contact; often the configuration of one side-chain which has been unambiguously established imposes limitations on nearby side-chains which help in their identification.

(4) Forking of the density in a side-chain can often be clearly seen, and the position of the fork greatly aids identification. Thus a side-chain forked at Cβ must be valine, threonine, or *iso*leucine; a side-chain forked at Cγ must be leucine, aspartic acid or a ring. The shape of the density at the fork is also diagnostic; thus tetrahedral forking at Cγ can only be leucine, while a planar fork must mean aspartic acid or a ring. Ring side-chains (His, Phe, Tyr, Try) can most easily be identified by means of special sections cut in their plane; some examples of these are shown in Fig. 1.

(5) Threonine and *iso*leucine possess a second asymmetric carbon atom, of known absolute configuration. This provides a valuable check on the identification of these two amino-acids.

Some ambiguities remain even when all these methods have been applied. For example, threonine and valine, glutamic acid and glutamine, aspartic acid and asparagine, cannot be distinguished by shape alone; and leucine and aspartic acid, histidine and phenylalanine, are often difficult to distinguish at the present resolution. It is sometimes possible, however, to discriminate between these pairs by looking for interactions with nearby groups. Thus threonine, aspartic acid and histidine can interact with neighbours by means of hydrogen bonds or salt bridges, while valine, leucine and phenylalanine cannot approach nearby groups more closely than is permitted by Van der Waals contacts, which are definitely longer (see, for example, Fig. 1). Another difficulty arises from the fact that a side-chain can sometimes assume two alternative configurations between which it is statistically distributed in different molecules in the crystal. Thus we have found several lysines which can interact with either of two nearby groups, each configuration being correctly staggered; such a lysine appears to be branched and may easily be mistaken for a forked side-chain. Quite apart from these difficulties, the experimental errors inherent in the present Fourier synthesis often make identification difficult; these errors are particularly large near the sites of heavy-atom substitution. Identification is also more difficult in the non-helical parts of the molecule, where the configuration of the main chain is difficult to establish with certainty; and it is difficult to identify side-chains, especially longer ones, which stick out of the molecule into the ambient solution, presumably because they can assume several alternative configurations.

The process of identifying side-chains involves locating precisely, first the main chain atoms to which the side-chains are attached, and secondly, the atoms of the side-chains themselves. These atomic co-ordinates will also be required for structure factor calculations in refining the structure at higher resolution. In all, we have located with reasonable precision (~¼ Å.) 634 atoms in helical regions of the main chain and in the haem group, and 262 atoms in side-chains which have been identified fairly definitely; excluding hydrogens the molecule contains a little more than 1,200 atoms, so, at a conservative estimate, it should be possible to include in the initial structure factor calculations some 75 per cent of the atoms in the structure.

Correlation between X-ray and Chemical Data

Column 1 of Table 1 summarizes the results of a detailed survey of the side-chains, our degree of confidence in each identification being indicated numerically. In all, 151 residues have been located, whereas the chemical analysis indicates a total of 153. There are eight segments of α-helix, indicated by the letters *A*–*H*; these are separated by non-helical regions *AB*, *CD*, *EF*, etc. So far as we have been able to determine, all the α-helical segments are straight and regular with the exception of *E*, which has a slight but definite bend in the middle.

In column 2, all sixteen tryptic peptides identified by Edmundson and Hirs (see previous article) have been placed alongside corresponding regions of the polypeptide chain, four of them with less confidence than the others. In general, the composition of each peptide determined from the model agrees with that found chemically, as does the sequence (wherever it has been established by Edmundson and Hirs), and the preliminary evidence which they have obtained from the chymotryptic digest as to the order in which the tryptic peptides are connected is confirmed by our placing. Once the peptides have been placed, their known chemical compositions can be used to discriminate between alternative X-ray identifications of particular side-chains, but there remain a few absolute discrepancies which are indicated in Table 1; it must be emphasized that both the X-ray and the chemical data are preliminary, so that some discrepancies and errors

Table 2

	Total composition				Core	
	X-ray identification			Chemical	X-ray	Chemical
	(*a*)	(*b*)	(*c*)			
Gly	8	9	11	11	3	3
Ala	13	14	17	17	3	3
Ser	3	4	6	6	3	3
Val	0	1	6	8	4–5	6
Thr	2	2	5	5	1	1
Ileu	4	5	8	9	3–4	4
Leu	8	10	15	18	8	7–8
Asp	2	5	8	8	—	—
Glu	8	11	17	19	4	5
Lys	6	11	18	19	3	3
Arg	2	3	4	4	1	1
Pro	4	4	4	4	—	—
His	5	5	10	12	3	4–5
Phe	6	6	6	6	1	1
Tyr	3	3	3	3	1	1
Try	2	2	2	2	2	2
Met	2	2	2	2	—	—
Unallocated			0		4	
Totals	78	97	151	153	45	44–46

(*a*) Identified with confidence 5 or 4 (see notes to Table 1) from X-ray data alone.
(*b*) *a* + residues identified from X-ray evidence with help from composition of tryptic peptides which can be placed with confidence (ordinary type in Table 1).
(*c*) Best allocation of residues, taking into account overall chemical composition as well as chemical evidence included under *b*.
Notes. (i) In the allocations in columns *b* and *c*, there are: 16 residues where chemical evidence has been used to select from two equally probable X-ray identifications; 8 residues where chemical evidence has been used to select a less probable from two or more X-ray identifications; 6 residues allocated purely on the basis of chemical evidence (no identification possible from X-ray evidence); 4 absolute discrepancies between X-ray and chemical evidence (see Table 1).
(ii) The figures in columns (*a*) and (*b*) are often reduced by difficulties in distinguishing particular pairs; thus if Val and Thr are taken together, the figures are *a* 8, *b* 11, *c* 11 (chemical analysis, 13).

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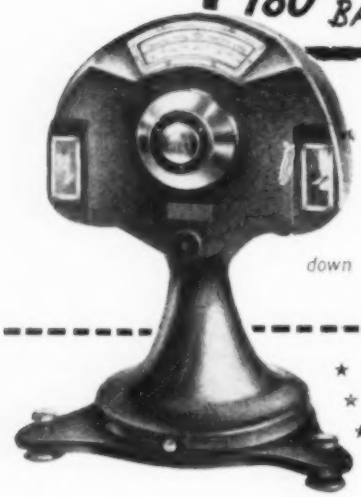

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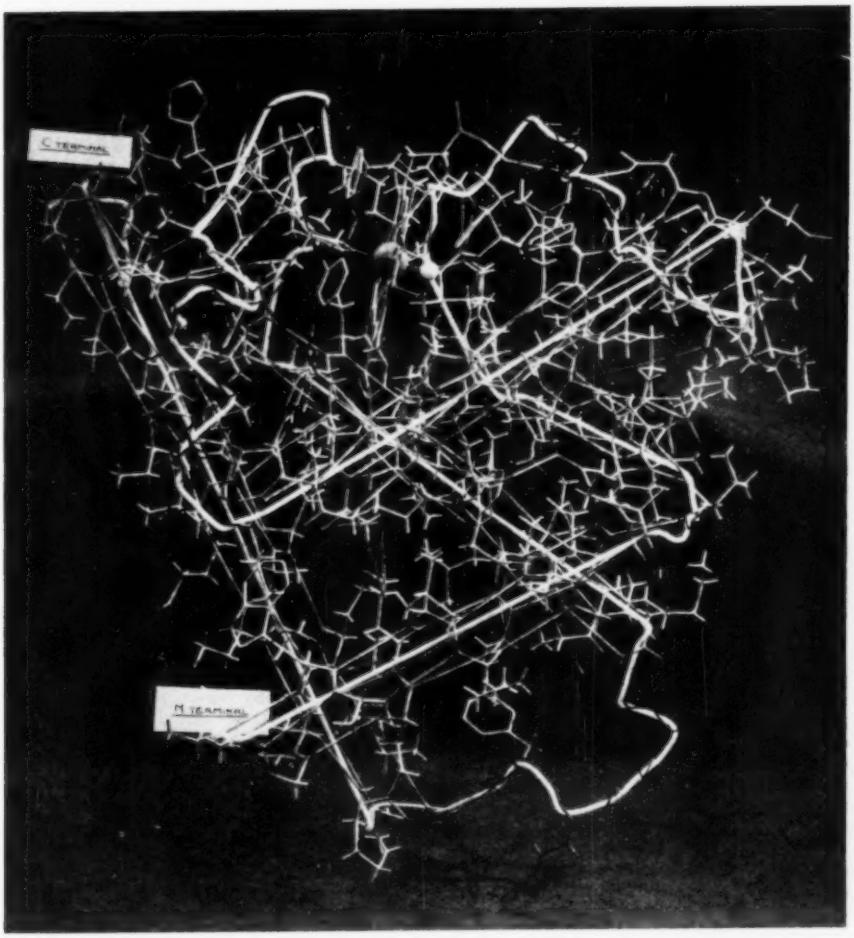

Fig. 2. Model of the myoglobin molecule, including side-chains. The course of the main chain is indicated by a white cord, the N-terminal and C-terminal residues being marked. The iron atom is shown as a grey sphere; the nearby white sphere is a presumed water molecule co-ordinated to it

must be expected. The overall agreement between the X-ray and chemical data as regards total amino-acid composition is summarized in Table 2.

In many cases our assignment of tryptic peptides to particular regions of the sequence was made in advance of more detailed chemical evidence obtained later by Edmundson and Hirs, which in all cases confirmed the assignment. Thus, the sequence of the residues within peptides 11, 15, 17 and 20 was determined chemically after these peptides had been placed as indicated in Table 1; again, the evidence from chymotryptic digestion suggesting the peptide sequences 1–11–8–16 and (part of core)–20–2–6 was not known to us at the time these peptides were similarly arranged on the basis of X-ray evidence.

One major problem concerns the placing of the so-called core, which we have tentatively assigned to the regions indicated in Table 1. As shown in the preceding article by Edmundson and Hirs, tryptic digestion leaves an insoluble core of 44–46 residues. By the usual tests the core possesses a single terminal amino-group which corresponds to that of the intact molecule; accordingly we tried to fit it to the first 44–46 residues (from *A*1 to about *CD*5) at the amino-end of the chain. This arrangement led to several difficulties, however. Thus, the overall composition of this region, determined from the model, does not correspond to that of the core; again, no satisfactory places can be found for peptides 20, 2 or 6; and finally, residue *C*2, which is only 35 places from the end of the chain, is almost certainly proline, an amino-acid which the core is believed to lack. These difficulties could be resolved if it was assumed that the core consisted of two parts, one comprising residues *A*1–*B*15, and the other residues *G*4–*G*16. The total composition of these regions agrees rather well with that of the core (see Table 2); peptides 20, 2 and 6 can be placed naturally from *B*16 to *CD*5 inclusive, and the sequence (part of core)–20–2–6 agrees with Edmundson and Hirs's deductions from the chymotryptic digest; on the other hand, we meet a new and still unresolved difficulty, namely, as yet there is no chemical evidence of a second amino end-group in the core. We may also ask why, if the core indeed consists of two fragments, these should remain

stuck together during prolonged digestion. It may be noted that in the intact molecule the two regions assigned to the core pass close to one another, and it may be that some unusual type of chemical bond is involved (we have in fact observed a continuous bridge of high electron density between residues *A*11 to *G*16 which might conceivably include such a bond).

Some Features of the Structure

Fig. 2 is a photograph of a model of the molecule, including side-chains and viewed from about the same angle as Fig. 5 of the previous article[1].

Corner turning. The molecule contains eight non-helical regions, one of which consists of four residues at the carboxyl end of the chain, while the others form corners between lengths of helix. Each corner is different from every other, and the numbers of residues contained in them varies from 0 to 8. It is well known that proline cannot be inserted into an α-helix except at its amino-end, so it is not surprising to find that all four prolines in the molecule are in different corners at the last turn of a helix; one of these corners (*BC*) is very elegant, in that it contains no non-helical residues—every residue forms part of either helix *B* or helix *C*. (Another corner which contains no non-helical residues is *DE*, but there is no proline in this region.) Two other types of interaction, which are evidently important in determining the configuration of a corner, have been observed: (1) the hydroxyl group of serine (*E*1) or threonine (*D*1) hydrogen-bonding to a free peptide imino-group at the amino-end of a helix, and (2) a lysine (*B*7), which originates from quite a different part of the molecule, bonding to a free peptide carbonyl group in corner *DE*. It is by no means obvious, however, what interactions are primarily responsible for the existence of several of the corners. The three-dimensional configuration of a protein is presumably determined by the position and nature of the corners, and eventually one might hope to be able to deduce these from a study of the amino-acid sequence. The variety and complexity of the non-helical regions in myoglobin suggest, however, that this will be by no means a simple matter.

Environment of the haem group. It is nearly certain that the group which links the iron atom to the protein is histidine (*F*8). On the distal side of the iron atom is a single peak, presumably a water molecule; beyond this is a side-chain (*E*7) which is probably histidine or perhaps glutamic acid (or glutamine). As might be expected, the polar propionic acid groups lie on the outside of the molecule, one probably linked to arginine (*CD*3); on the other hand, the non-polar vinyl groups are buried deep in the interior. The whole inner part of the haem group is surrounded by non-polar side-chains, and it is noteworthy that there is a large concentration of aromatic side-chains in the general neighbourhood of the haem group.

General distribution of side-chains and liquid. There is a tendency, perhaps less marked than might have been expected, for polar side-chains to project outwards from the molecule and for non-polar ones to be buried within it; 30 per cent of the polar and 45 per cent of the non-polar residues are buried. This tendency is much more obvious in certain side-chains, especially larger ones; thus all the phenylalanines and methionines are internal, and almost all the lysines, arginines and glutamic acids are external. On the other hand, most of the non-polar alanines project outwards.

Nearly all polar groups, including peptide carbonyl and imide groups, interact either with nearby groups or else with isolated peaks which must be water molecules or ions. Most of these isolated peaks are external; there are, apparently, a few water molecules within the protein molecule, but for the most part the protein is close-packed with little internal free space. The ambient fluid is 4 *M* ammonium sulphate; it is probable that the lattice contains 20–30 ammonium sulphate molecules per myoglobin molecule. Ammonium ions would be indistinguishable from water molecules at the present resolution; on the other hand, sulphates would appear as dense peaks if they occupied defined positions in the lattice. We have actually observed only two or three peaks on the surface of the molecule which are dense enough to be certainly sulphate ions; the fact that the other sulphate ions are not observed suggests that most of them, together with the water in which they are dissolved, are distributed at random.

We wish to thank the Director of the Mathematics Laboratory, University of Cambridge, for facilities on *Edsac* Mk. II; the Rockefeller Foundation for generous financial support; the National Science Foundation (U.S.A.) and National Institutes of Health (U.S.A.) for providing fellowships for one of us (R. E. D.); Dr. Joyce Wheeler for preparing *Edsac* programmes used in making special Fourier sections; Miss Mary Pinkerton, Mrs. J. Blows, Mrs. V. Cotterill, Miss J. Leeland, Mr. P. Mulhall and Miss E. Rowland for assistance in model building and in other ways.

[1] Kendrew, J. C., Dickerson, R. E., Strandberg, B. E., Hart, R. G., and Davies, D. R., *Nature*, **185**, 422 (1960).

Comparison Between the Amino-Acid Sequences of Sperm Whale Myoglobin and of Human Hæmoglobin

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PERUTZ *et al.* have shown that the tertiary structures of the α- and β-chains of horse hæmoglobin closely resemble those of sperm whale myoglobin[1]. One might predict that there would be correspondences between those side-chains, the specific interactions of which are responsible for the tertiary structures of the three types of chain, and for the closely similar reactions of the two proteins with oxygen and other ligands, even though there are substantial differences between their overall amino-acid compositions. Unfortunately, the amino-acid sequence of horse hæmoglobin has not yet been determined, but most of that of human hæmoglobin has recently been established by Braunitzer *et al.*[2-4],

Table 1

	Hæmoglobin α-	Hæmoglobin β-	Myoglobin	
1		Val		
2	Val	His		
3	*Leu*	*Leu*		
4	Ser	Thr	Val	*A1*
5	Pro	Pro	Ala	2
6	Ala	Glu (*e*) (*f*)	Gly	3
7	Asp	*Glu* (*g*)	*Glu*	4
8	*Lys*	*Lys*	Try	5
9	Thr	*Ser* (*l*)	*Ser*	6
10	Asp	Ala	Glu	7
11	*Val*	*Val*	Ileu	8
12	Lys	Thr (*m*)	Leu	9
13	*Ala*	*Ala*	Lys	*10*
14	Ala	Leu	?	11
15	*Try*	*Try*	*Try*	12
16	*Gly*	*Gly*	?	13
17	*Lys* (*a*)	*Lys*	Leu	14
18	*Val*	*Val*	Leu	15
19	Gly	Asp	Glu	16
20	Ala	|	?	*AB1*
21	His	|	Leu	*B1*
22	Ala	*Val*	*Val*	2
23	Gly	Asp	Ala	3
24	*Glu*	*Glu* (*n*)	Gly	4
25	Tyr	Val	His	5
26	*Gly*	*Gly*	*Gly*	6
27	Glu	Gly	Lys	7
28	Ala	Glu (*b*)	Leu	8
29	*Ala*	*Ala*	Thr	9
30	*Leu*	*Leu*	*Leu*	10
31	Glu	Gly	Ileu	11
32	*Arg*	*Arg*	Ser	12
33	Met	*Leu*	*Leu*	13
34	*Phe*	Leu	*Phe*	14
35	Leu	Val	Lys	15
36	*Ser*	Val	*Ser*	16
37	Phe	Tyr	His	*C1*
38	Pro	Pro	Pro	2
39	Thr	Glu	Glu	3
40	*Thr*	Thr	*Thr*	4
41	Lys	Try	Leu	5
42	Thr	Arg	Glu	6
43	Tyr	Phe	Lys	7
44	Phe	*Phe*	*Phe*	*CD1*
45	Pro	Glu	Asp	2
46	His	Ser	Arg	3
47	Phe	*Phe*	*Phe*	4
48	Gly	Gly	Lys	5
49	His	Asp	His	6
50	Leu	*Leu*	*Leu*	7
51	Ser	Ser	Lys	8
52	Ser	*Thr* (*o*)	*Thr*	*D1*
53	|	Pro	Glu	2
54	|	Asp	Ala	3
55	|	Ala	Glu	4
56	|	Met	Met	5
57	|	Val	Lys	6
58	|	Gly	Ala	7
59	Asp	Asp	Ser	*E1*
60	Ala	Pro	Glu	2
61	Glu	Lys	Asp	3
62	*Val*	*Val*	Leu	4
63	*Lys*	*Lys*	*Lys*	5
64	Gly (*b*)	Ala	Val	6
65	*His* (*c*)	*His* (*i*)	(*His*, Glu)	7
66	*Gly*	*Gly*	*Gly*	8
67	*Lys*	*Lys*	Ileu	9
68	*Lys*	*Lys*	Glu	10
69	*Val*	*Val* (*j*)	*Val*	11
70	Ala	Leu	Asp	12
71	Asp	Gly	(Glu, His)	13
72	Ala	*Ala*	*Ala*	14
73	*Leu*	Phe	*Leu*	15
74	Thr	Ser	Gly	16
75	Asp (*d*)	Asp	Ala	17
76	Ala	Gly	Ileu	18
77	Leu	Leu	Asp	19
78	Ala	Ala	Arg	20
79	His	His	|	
80	Leu	Leu	|	
81	Asp	Asp	|	
82	Asp	Asp	|	
83	|	Leu	Lys	*EF1*
84	|	*Lys*	*Lys*	2
85	|	*Gly*	*Gly*	3
86	|	Thr	Leu	4
87	Met	Phe	His	5
88	Asp	Glu	Glu	6
89	Leu	Leu	Leu	7
90	Asp	Asp	Glu	8
91	Ser	Glu	Glu	*F1*
92	Ala	Ala	Ala	2
93	Pro	Pro	Pro	3
94	Val	Thr	Thr	4
95	Ala	Ala	Ala	5
96	Val	Val	His	6
97	Ser	Ser	Ser	7
98	*His*	His	*His*	8
99	*Ala*	CysH	*Ala*	9
100	His	His	|	
101	*Lys*	Lys	*Lys*	*FG1*
102	*Leu*	Leu	*Leu*	2
103	Arg	Leu	Phe	3
104	Val	Val	Lys	4
105	Asp	Asp	Ileu	5
106	Pro	Pro	Pro	*G1*
107	Val	Leu	Ileu	2
108	Asp	Asp	Lys	3
109	*Phe*	*Phe*	Tyr	4
110	Lys	Arg	?	5
111	*Leu*	*Leu*	Glu	6
112	Leu	Asp	His	7
113	Leu	Leu	Leu	8
114	Ser	Gly	Ser	9
115	Leu	Leu	?	10
116	Ala	Val	Ala	11
117	Val	Val	Val	12
118	Leu	Leu	Ileu	13
119	His	His	His	14
120	Val	Val	Val	15
121	Ala	Phe	Arg	16
122	Ala	Ala	Ala	17
123	Thr	Gly	Thr	18
124	CysH	CysH	Lys	19
125	His	His	His	*GH1*
126	|	|	Asp	2
127	His	Lys	Asp	3
128	Glu	*Glu* (*k*)	*Glu*	4
129	Phe	*Phe*	*Phe*	5
130	Thr	Thr	Gly	6
131	Pro	Pro	Ala	*H1*
132	Pro	Pro	Pro	2
133	Ala	Val	Ala	3
134	Leu	Glu	Asp	4
135	Ala	Ala	Gly	5
136	Ser	*Ala*	*Ala*	6
137	Leu	Tyr	Met	7
138	Asp	Glu	Gly	8
139	*Lys*	*Lys*	*Lys*	9
140	Phe	Val	Ala	10
141	Val	Val	Leu	11
142	Val	Val	Glu	12
143	Ala	Ala	Leu	13
144	Thr	Ala	Phe	14
145	Ser	Gly	Arg	15
146	Ser	Ala	Lys	16
147	Leu	Asp	Asp	17
148	Leu	Leu	Ileu	18
149	Thr	*Ala*	*Ala*	19
150	Ser	His	Ala	20
151	*Lys*	*Lys*	*Lys*	21
152	*Tyr*	*Tyr*	*Tyr*	22
153	Arg	His	Lys	23
154			Glu	24
155			Leu	*HC1*
156			Gly	2
157			Tyr	3
158			Gly	4
159			Glu	5

Notes. The amino-acid sequence given for myoglobin is that which is considered to be the most probable on the basis of X-ray and chemical evidence.

Non-ordered regions of the hæmoglobin chains are enclosed in boxes.

Corresponding residues in the ordered regions of the chains are italicized; but all prolines are printed in heavy type.

Substitutions: in the α-chain, hæmoglobin *I*: Asp at (*a*), ref. 6; Norfolk: Asp at (*b*), ref. 7; *M* (Boston): Tyr at (*c*) (Gerald, P. S., Efron M. L., Jones, jun., S. H., and Pisciotta, A. V., personal communication); *G* (Philadelphia): Lys at (*d*), ref. 8. In the β-chain, hæmoglobin *S*: Val at (*e*), ref. 6; *C*: Lys at (*f*), ref. 6; *G* (San José): Gly at (*g*), ref. 6; *E*: Lys at (*h*), ref. 6; *M* (Emory): Tyr at (*i*) (Gerald, P. S., Efron, M. L., Jones, jun., S. H., and Pisciotta, A. V., personal communication); *D* (Punjab) (= *D*): Glu.N at (*k*) (Baglioni, C., personal communication). In the δ-chain: Thr at (*l*), ref. 9; Asp at (*m*), ref. 9; Ala at (*n*), ref. 9; Ser at (*o*), ref. 9.

by Hill and Konigsberg[7], and by Schroeder and Jones, and it is reasonable to expect correspondences here, too, in view of the accumulating crystallographic evidence that the tertiary structures of haemoglobins and of myoglobins of different species are very similar.

In Table 1 the human haemoglobin chains have been placed alongside that of myoglobin (see preceding article by Kendrew *et al.*) in what seems to us the most plausible manner. The chains differ in length (myoglobin 151–153 residues, haemoglobin α-chain 141 and β-chain 150 residues), and in comparing them we have tentatively assumed that interpolations or deletions occur only in or near inter-helical regions, since even a single change of this kind in the middle of a helix would completely alter the environments of all the side-chains on at least one side of the change. There are substantial regions in both haemoglobin chains where the sequence of residues has yet to be determined; in each non-ordered region, we have arranged residues so that, where possible, amino-acids coincide with identical residues in the other haemoglobin chain; where that cannot be done, or where corresponding regions in both haemoglobin chains are non-ordered, the haemoglobin residues have been arranged so as to correspond as nearly as possible to residues in the myoglobin chain. The fourth column of the table indicates those regions of the myoglobin chain which are α-helical (for terminology see Table 1 of the preceding article); the first column contains a numbering system which will be used for reference in the present article.

The tentative scheme in Table 1 leads to the following conclusions:

(1) All the prolines in the α- and β-chains can be placed so as to lie at the open end of a helix or in a non-helical region; wherever proline occurs in myoglobin, a proline can be correspondingly placed in both α- and β-chains. Sharp corners (that is, with few or without non-helical residues) do not, however, require the presence of proline; corner *AB* is without proline in any of the three chains, and *DE* has no proline in myoglobin, although it apparently has the same shape in the β-chain[1], which has proline at this position.

(2) Side-chains, the identities of which in myoglobin appear to be determined by specific interactions or steric features, often have counterparts in the haemoglobin chains. Thus, at residues 26 and 66, helices *B* and *E* approach one another so closely that no side-chain larger than glycine would be possible; glycine is found in each position in all three chains. Residue 65 in myoglobin is probably histidine, and if so is within hydrogen-bonding distance of a water molecule attached to the sixth co-ordination position of the iron atom; histidine appears at the same position in both haemoglobin chains. (The haem-linked residue in myoglobin is also histidine, residue 98. Unfortunately, the corresponding region of one of the two haemoglobin chains is still non-ordered; it is, however, possible to place histidines in position 98 in both α- and β-chains.) In myoglobin, the tyrosine at residue 152 forms a hydrogen bond with the main-chain carbonyl group of residue 105, presumably acting as a stabilizing bridge between the ends of the long helices *G* and *H*; tyrosines occur in the corresponding places in the α- and β-chains.

(3) The two haemoglobin chains, unlike that of myoglobin, each has a small non-helical tail (2 residues in the α-chain, 3 in β-) at the amino-end, helix *A* being terminated at the proline in position 5. On the other hand, the non-helical tail at the carboxyl end of the myoglobin chain is absent from both haemoglobin chains. Furthermore, in the α-chain of haemoglobin (but not in the β-) six residues are missing between residues 42 and 59, that is, in the region near the short helix *D*. Inspection of Perutz's 5·5-Å. model of horse haemoglobin confirms that in the α-chain the loop between 42 and 59 is shorter than in myoglobin or in the β-chain; this model also confirms that a 'tail' is present at the amino-end, and absent at the carboxyl-end, of each chain (Perutz, personal communication).

(4) Several of the substitutions which have been located in the δ-chain of haemoglobin A_2 and in the abnormal haemoglobins are indicated in Table 1. In nearly all cases these residues stick outwards from the molecule, so substitutions would not be expected to affect the tertiary structure. The only exceptions are the change from Thr to Ser at residue 52 in the δ-chain and the very interesting haemoglobin *M* substitutions. The former residue is important in terminating helix *D* (see preceding communication), and is Ser in α and δ, and Thr in β and myoglobin. The characteristic abnormality of haemoglobin *M* is an unusual difficulty in reducing the ferric to the ferrous form; in two variants we find that His has been converted to Tyr, in one case on the α-chain and in the other on the β-chain, at residue 65, which is located close to the iron atom opposite the haem-linked histidine (see (2) above). In the third variant, Val at residue 69 becomes Glu; this residue is also very close to the iron atom.

If non-ordered residues in the haemoglobin chains are disregarded, there are 50 possibilities for triple correspondences (identical residues in corresponding positions in all three chains)—only 10 (20 per cent) are observed. There are 54 possibilities of double correspondences between α- and β-, of which 26 (48 per cent) are observed; on the other hand, of 70 possible double correspondences between α- and myoglobin, only 20 (28 per cent) are found, and of 91 between β- and myoglobin only 25 (28 per cent). The main impression is that in spite of presumed close resemblances in tertiary structure, the correspondences are remarkably few. It must be concluded from this and the preceding article by Kendrew *et al.* that the crucial interactions which determine the tertiary structure of a protein are very complicated and are not confined to the corners between helices; detailed investigations, perhaps including comparisons between related proteins, will be necessary before general principles become apparent.

We thank Dr. M. F. Perutz for valuable discussions; also Drs. V. M. Ingram, Park S. Gerald and W. Konigsberg for a discussion of the (unpublished) proceedings of the Hæmoglobin Structure Workshop at Endicott House on December 14–16, 1960.

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THE ENGINEER IN COMMONWEALTH DEVELOPMENT

A LITTLE reflexion might suggest that it is perhaps a strange way to honour the achievements of distinguished men by inviting them to accept a presidency which involves a presidential address before a distinguished, but highly critical, audience or to give a named lecture which, because of the special circumstances, likewise attracts wide publicity. Many a famous scientist has emerged from such an ordeal with an impaired rather than an enhanced reputation; the specialist venturing outside the sphere in which he is an acknowledged master is too often apt to be trite or banal. On the other hand, such an occasion affords a great opportunity to present to an influential audience a considered synthesis which may well bear important fruit.

H.R.H. the Duke of Edinburgh is one who rises magnificently to such occasions. No one who heard his presidential address to the British Association at Edinburgh in 1951 could doubt his ability to take the broad, balanced view, based with meticulous care on carefully collected and assimilated facts, and to present his material in such a way as to shame the professional lecturer. This year he was invited jointly by the three great engineering institutions—the Civil, Mechanical and Electrical—to give the seventh Graham Clark Lecture on April 13. The first plan was a survey of "Resources, Human and Material, of the Commonwealth". The basic material was assembled and has been published as a series of statistical tables separately printed as appendixes to the lecture. A wide range of standard sources—in each case the best available—has been used and combined with the results of a number of specific inquiries (especially through the Commonwealth Economic Committee). Throughout these tables the emphasis is on a comparison between the Commonwealth (with countries separately named but including at this date the Union of South Africa) and the world as a whole. Population, labour force, land use, value of agricultural produce, energy production and consumption, primary production, mineral output, mineral reserves, transport and education are included in turn. The whole affords a simple yet effective view of how the Commonwealth stands in relation to the world as a whole.

But, as the Duke so rightly says, "resources are not very interesting until you start doing things to them". Since engineers play a dominant part in this, "I have tried to outline the engineer's part in the various fields of development and some of the opportunities and problems" of the profession. "The engineer is in fact the means by which the people are able to enjoy the fruits of science, whether in building new projects, or in maintaining and keeping up to date what is already in existence."

It is rumoured that the presidential address to the British Association was composed—and that is the right word—on the backs of naval signal forms during moments of hard-earned leisure in the chart room or on the bridge of a ship of the Royal Navy on active service. Incredible as it may seem that there were in fact moments of leisure during the recent royal tour to India and Pakistan, by his own confession the Graham Clark Lecture was similarly composed. One result is a particularly felicitous blend of library research and field observations. It may truthfully be said that no living person is better equipped to produce such a survey. No one has travelled the Commonwealth, from Antarctic to tropics, more widely yet always on duty, his hosts ever anxious to show everything worth while, their guest, always alert to note and record, not so much the detail, as the overall picture.

How does the Commonwealth stand in relation to the rest of the world? With 23 per cent of the land surface and 24 per cent of the population, the existence of 44 per cent of the land unused is a challenge since in food production the figures are not impressive. Only rice (24 per cent), barley (20 per cent) and mutton (23 per cent) are produced in proportion to land and population. It is freely admitted that the picture of the Commonwealth as a whole is distorted by the extreme contrasts between its constituent parts such as Britain and India, and the fact that India–Pakistan have 68 per cent of the total people. Nevertheless, the conclusion seems inevitable that the Commonwealth is at present not producing according to potential. 20 per cent of the world's rain falls on Commonwealth lands; Kariba and Volta are projects now in hand but the Hamilton Falls are unused and, taking energy as a whole—coal, oil, water-power—the Commonwealth's share in output is less than 12 per cent.

His Royal Highness comments, somewhat ruefully, that he has to bear criticism rather more frequently than most, and suggests that a little mild and well-intentioned criticism should be treated as a sign-post rather than as a slander. His comments, though forthright, are scarcely criticisms and are so obviously sincere and well-founded as to command respect. There is the old argument involving 'pure' and 'applied' science—by implication the latter also 'impure'—and it is still true that academic honours, for example, the fellowship of the Royal Society, are more hardly won by the applied scientist. Yet who deserves the greater credit: he who conceives an idea in a laboratory or he who with infinite pains adapts and refines it to the benefit of countless numbers of mankind? "We are apt to forget that much scientific research is only possible with the aid of very advanced engineering; computers, electron microscopes . . . are no longer bits of apparatus that can be knocked up in the lab." It is refreshing, too, to be reminded that our united aim should be to benefit mankind. "Unless large-scale projects and modernization plans are based upon a practical humanity they will contribute very little to man's progress." Or again, "it is becoming increasingly popular to look upon industry merely as a convenient way of giving employment . . . it has to satisfy the needs and desires of the individual". It is clear the Duke would not happily agree with those who go so far as to declare that the possession of resources is of little importance compared with the possession of capital with which to develop them. Such a view is economic colonialism at its worst and, by not

referring to either political or economic aspects of development, he makes the obvious assumption that mankind should be the master and not the slave of its own social and economic systems.

Coming from a world traveller, we have timely reminders of the importance of communications and of scale so difficult to judge in small countries such as Britain—five times as far across mainland Canada and twice as far from Bombay to Calcutta as from John o'Groats to Land's End.

Seeing the Duke's interest in youth, it is not surprising that he is far from happy regarding the adequacy of higher education in technical fields. The appeal for forward thinking is well timed and, like every other aspects of life brought into this stimulating address, merits the closest attention.

L. Dudley Stamp

THE U.S. ACADEMY OF SCIENCES

OFFICERS, MEDAL AWARDS AND NEW MEMBERS

DR. J. A. STRATTON, president of Massachusetts Institute of Technology, has been elected to a four-year term as vice-president of the U.S. National Academy of Sciences. Dr. G. B. Kistiakowsky, Abbott and James Lawrence professor of chemistry, Harvard University, and Dr. Kenneth B. Raper, professor of bacteriology and botany, University of Wisconsin, have been appointed members of Council for a term of three years.

The following medal awards have been made: the *Henry Draper Medal*, for original investigation in astronomical physics, to Dr. Martin Schwarzschild, Princeton University Observatory; the *Daniel Giraud Elliot Medal*, for meritorious work in zoology or palaeontology published each year, to Philip J. Darlington, jun., Museum of Comparative Zoology, Harvard University; the *Kimber Genetics Medal*, for achievement in the science of genetics, to Prof. J. B. S. Haldane, (recently) Indian Statistical Institute, Calcutta; the *Jessie Stevenson Kovalenko Medal*, for contributions to medical science, to Dr. K. F. Meyer, George Williams Hooper Foundation, University of California; the *Mary Clark Thompson Medal*, for services to geology and palaeontology, to Dr. Norman D. Newell, American Museum of Natural History; the *James Craig Watson Medal*, for noteworthy discoveries or research in astronomy, to Prof. Otto Heckmann, Hamburg-Bergedorf Observatory.

The following new members have been elected: Prof. D. I. Arnon, professor of plant physiology, University of California; Dr. W. O. Baker, vice-president in charge of research, Bell Telephone Laboratories; Prof. S. Benzer, professor of biophysics, Purdue University; Dr. H. A. Borthwick, principal plant physiologist, Agricultural Research Service, U.S. Department of Agriculture; Prof. R. H. Burris, professor of biochemistry, University of Wisconsin; Prof. Shiing-Shen Chern, professor of mathematics, University of California at Berkeley; Dr. P. E. Cloud, jun., chief, Paleontology and Stratigraphy Branch, U.S. Geological Survey; Prof. J. H. Comroe, jun., director of the Cardiovascular Research Institute and professor of physiology, University of California Medical Center; Prof. D. J. Cram, professor of chemistry, University of California; Prof. J. F. Crow, professor of zoology and genetics, University of Wisconsin; Dr. L. S. Darken, associate director, research laboratory, United States Steel Corporation; Prof. C. Djerassi, professor of chemistry, Stanford University; Prof. W. Von Eggers Doering, professor of chemistry, Yale University; Prof. R. Dulbecco, professor of biology, California Institute of Technology; Prof. A. I. Hallowell, professor of anthropology, University of Pennsylvania; Prof. B. L. Horecker, professor of microbiology, New York University College of Medicine; Prof. R. D. Hotchkiss, member, and professor of cellular physiology, Rockefeller Institute; Dr. Libbie H. Hyman, research associate, American Museum of Natural History; Prof. M. G. Inghram, professor of physics, University of Chicago; Prof. W. N. Lipscomb, jun., professor of chemistry, Harvard University; Dr. H. F. Mark, director, Polymer Research Institute, Polytechnic Institute of Brooklyn; Prof. H. Neurath, professor of biochemistry, University of Washington; Prof. G. E. Palade, member, and professor of cytology, Rockefeller Institute; Prof. R. V. Pound, professor of physics, Harvard University; Prof. L. A. Riggs, professor of physiological psychology, Brown University; Dr. R. B. Roberts, chairman, Biophysics Section, Department of Terrestrial Magnetism, Carnegie Institution of Washington; Prof. Per F. Scholander, professor of physiology, Scripps Institution of Oceanography; Dr. C. D. Shane, astronomer, Lick Observatory; Prof. D. C. Spencer, professor of mathematics, Princeton University; Mr. H. M. Stommel, research associate in physical oceanography, Woods Hole Oceanographic Institution; Prof. Leo Szilard, professor of biophysics, University of Chicago; Prof. J. W. Tukey, professor of mathematics, Princeton University; Prof. F. T. Wall, research professor of physical chemistry, University of Illinois; Dr. A. M. Weinberg, director, Oak Ridge National Laboratory; Prof. J. H. Williams, professor of physics, University of Minnesota.

OBITUARIES

Sir William Savage

The death of Sir William Savage in his eighty-ninth year on April 6, 1961, means the passing of the last survivor of that distinguished company of medical officers of health who contributed so largely to the progress of public health in the late nineteenth and early part of the present century.

William George Savage, the son of John H. Savage, was born in Jamaica in 1872. He was educated privately, at University College, London, and University College Hospital. He took the B.Sc.(Lond.)

in 1894, the M.B.Lond. with honours in medicine and the gold medal in forensic medicine in 1896, the diploma in public health in 1897 and the M.D.(Lond.) in 1898. After a resident post at the Royal Sussex Hospital, he became assistant professor of pathology in University College, London. From 1900–03 he was lecturer in pathology and public health at University College, Cardiff, and during 1903–09 medical officer of health and public analyst, Borough of Colchester. In 1909 he was appointed the first county medical officer of Somerset. Here he did the work that was to make him famous.

Savage was remarkable in that he continued to pursue bacteriological researches which gave him an international reputation, and at the same time administered the public health of his county with conspicuous success.

The organisms present in food poisoning early engaged Savage's attention, and he did research work for the Medical Research Council, partly in collaboration with Bruce White, into the serology of the *Salmonella* groups and their relation to food poisoning (*M.R.C. Reports*, Nos. 91 and 92, 1925). He also showed that domestic animals and vermin were the main reservoirs of these organisms. He made further fundamental studies into food poisoning. In 1940, in a discussion at the Royal Society of Medicine, he gave an account of some original work on *Salmonella dublin*, pointing out that it was responsible for human infection in a number of cases; and as late as 1956 he published a paper with evidence on problems of *Salmonella* food poisoning, and directed attention to the marked increase of food poisoning in Great Britain since the end of the Second World War (*Brit. Med. J.*, ii, 317; 1956).

Savage strongly advocated the pasteurization of milk; he wrote a report on milk and the public health in 1912, and published the following books: *The Bacteriological Examination of Food and Water* (1906), *Rural Housing* (1915), *Food and the Public Health* (1919) and *Food Poisoning and Food Infections* (1920). He was the author of a number of special reports to the Local Government Board, of papers on the prevention of human tuberculosis of bovine origin, on canned foods in relation to health, and on many other scientific subjects, the majority of which were based on his special investigations. He was Milroy Lecturer and Mitchell Lecturer at the Royal College of Physicians, president of the Society of Medical Officers of Health in 1935, examiner in public health for the Universities of London, Wales and Bristol, and received a knighthood for his distinguished services in 1938; in the same year the honorary degree of M.D.(Bristol) was conferred on him.

In 1937, Savage retired from the post of county medical officer but returned to assist in public health work in Somerset during the Second World War. Thereafter he did important work as chairman of the Ministry of Food's Catering Trade Working Party, while his advice and wisdom continued to be sought by other Government departments and public health bodies.

Savage was a strong man both physically and mentally. His interests were many. He played golf and lawn tennis up to an advanced age, was a daring swimmer and a keen gardener. Interested also in history and archæology, in retirement at Winchester, he published an important book, entitled *The Making of Our Towns*, in 1952 based on extensive research, and had been president of the Somerset Archæological Society in 1945. He was a staunch friend, kind and generous to many. Sir William married Mary A. M. Wilson in 1900, and they had a son and daughter. His son, Dr. S. W. Savage, is county medical officer of Warwickshire.

ARTHUR S. MACNALTY

Prof. Gideon Mer, O.B.E.

PROF. GIDEON GERONIMO MER, professor of epidemiology and director of the Malaria Research Station of the Hebrew University of Jerusalem, died on March 23, at the age of sixty-six, in Haifa. To malariologists all over the world he will be remembered for his work on the transmission of quartan malaria, for his method of determination of the age of mosquitoes—a technique now universally adopted in epidemiological studies of insect-borne diseases for a series of lucid papers on the bionomics of *A. elutus*, and for his studies of insecticides in recent years.

Prof. Mer was born in 1894 in Poniewez, Lithuania (at that time part of Czarist Russia). Both his parents were physicians. After graduating from the Real Gymnasium he went, in 1912, to study medicine in Heidelberg. He remained there only two years. At the call of the idealistic youth movement he interrupted his studies and went to Palestine.

At the outbreak of the First World War he was exiled by the Turkish authorities to Egypt. He joined the British Forces, fought in Gallipoli and elsewhere, and later returned to Palestine with the armies of Allenby. After demobilization he directed the first reclamation works in the malaria-infested valleys of Ezdraelon and Jordan.

In 1924, after a brief return to Lithuania, and following a happy marriage, Mer went back to his medical studies. He chose Italy, for he wanted to gain first-hand experience from the famous Italian school of malariologists of Grassi, Marchiafava and Celli. He graduated with honours in 1928, and after spending a year in postgraduate studies at the schools of tropical medicine in Amsterdam and Paris, he returned in 1929 to Palestine to direct the Malaria Research Station of the Hebrew University at Rosh-Pinah-Galilee, where he established free polyclinics for the Arab population of the region and soon was known as 'Hakim el Kabir', beloved and honoured by all.

Mer's research work was done under most difficult and exacting conditions. The experimental transmission of quartan malaria he carried out on himself and on his wife (volunteer Z. M.). The first trials on suppressive treatment of malaria with 'Cl.inoplasmin' were done in times of strife at the risk of his own life. During these pre-war years he also found time to serve as medical officer to British troops stationed in Galilee, to many of whom his home in the hills became well known.

With the outbreak of the Second World War, Mer volunteered, together with three of his assistants, to H.M. British Forces and commanded a malaria field laboratory in Iran, Iraq and Burma. He was made O.B.E. for his distinguished services and leadership.

After the War, he returned to Israel to use his newly acquired knowledge of modern insecticides for the reclamation of malarious areas. With the establishment of the State of Israel, he served with distinction on many health missions, as head of the Department of Preventive Medicine of the Armed Forces during the war of independence, and for a brief period as director-general of the Medical Services.

MEIR YOELI

NEWS and VIEWS

Assyriology in London : Prof. C. J. Gadd, C.B.E., F.B.A.

Prof. C. J. Gadd, who until his retirement in 1960 held the chair of Ancient Semitic languages and civilizations at the School of Oriental and African Studies, University of London, is certainly the leading Assyriologist in Britain, and one who is very highly esteemed by his colleagues abroad. His work in the field of Sumerian and Babylonian history and literature, as well as in Mesopotamian archæology, has earned him a world-wide—and fully justified—reputation. Born at Bath in 1893, Gadd was educated at King Edward VI School, Bath, and at Brasenose College, Oxford, served in the First World War, and joined the British Museum in 1919 as an assistant keeper in the Department of Egyptian and Assyrian Antiquities—now split into two independent departments, Western Asiatic Antiquities and Egyptian Antiquities. In 1948 he succeeded Sidney Smith as keeper of the Department, a post he held with great distinction until the year 1955, in which he was appointed to his chair at the University, again as the successor of his former colleague, Sidney Smith.

Besides numerous articles in scholarly journals and five volumes in the well-known series, *Cuneiform Texts from Babylonian Tablets in the British Museum*, Prof. Gadd has published several important works, including *A Sumerian Reading Book* (1924), now unfortunately out of print, and *The Stones of Assyria* (1936), a recognized standard book on the history of the first discoveries of Assyrian Palaces. Prof. Gadd has served on the staff of British archæological expeditions in Iraq (Ur, 1923–24; Nimrud, 1952) and Syria (Alalakh-Atshana, 1946). He was chairman of the Assyriological Section of the Twenty-third International Congress of Orientalists when it met at Cambridge in 1954. He was elected a Fellow of the British Academy in 1940, and was made C.B.E. in 1955. Two years earlier, Oxford conferred upon him the honorary degree of doctor of letters, and his former College elected him to an honorary fellowship.

New Chair of Assyriology

A chair of assyriology, as recently established in the University of London, has been long overdue in Britain. 'Assyriology' now includes, by convention, a group of studies concerning ancient western Asia, from the beginnings of civilization in those parts down to about the time of Alexander's conquests. Thus it comprises not only an assortment of languages, by no means all Semitic, but also a diversity of cultures over a span of three thousand years, their bond of union being, in general, the cuneiform script. At their outset these studies owed perhaps most of all to a few men of genius of British birth; yet a chair of assyriology by name has never hitherto existed. The new foundation replaces the former chair of ancient Semitic languages and civilizations.

Prof. D. J. Wiseman

Mr. D. J. Wiseman, the professor-designate, has already a notable career in the learned world. While assistant-keeper in the British Museum he has made his mark as an interpreter of cuneiform texts. From the later period of Babylon and Assyria he has published two sets of historical documents, *Chronicles of Chaldaean Kings* and *The Vassal-Treaties of Esarhaddon*, both with universal acceptance as definitive. From an earlier age and a provincial *milieu* he has made known *The Alalakh Tablets*, a patch of new ground which he opened with great success. Also to his credit are two widely circulated books upon Western Asiatic archæology. All who are interested in the peoples of the Ancient Orient will wish him, with confidence, a tenure of the chair as brilliant as it promises to be long.

Geophysical Research in the Meteorological Office

Dr. Frank Stacey has returned to the United Kingdom from the Research School of Physical Sciences in the Australian National University at Canberra to take up one of the two new Gassiot research fellowships in the Meteorological Office. He has written extensively on geomagnetism and will conduct his future researches from Edinburgh, where he will enjoy the advantages of close association with scientists of allied interests at the University and at Eskdalemuir Observatory near Dumfries. The latter has, for many years, been the centre of geomagnetic work in the Meteorological Office. Dr. H. M. Iyer has been appointed to the other fellowship. Dr. Iyer is at present working at the University of California and will take up his new appointment in the autumn, when he will work from Kew Observatory on the increasingly important subject of seismology.

C.S.I.R.O. Wildlife Survey Section : Mr. H. J. Frith

Mr. H. J. Frith has been appointed officer-in-charge of the Wildlife Survey Section of the Commonwealth Scientific and Industrial Research Organization (Australia). He succeeds Mr. F. N. Ratcliffe, who resigned last year to become assistant chief of the Organization's Division of Entomology. Mr. Frith graduated in agricultural science from Sydney in 1941. During the rest of the War he served in the Middle East and New Guinea and won a commission. He joined the Organization after his demobilization in 1946 as an assistant research officer at the Irrigation Research Station, Griffith, New South Wales. He remained at Griffith for five years, engaged on horticultural research on citrus problems. He transferred to the Wildlife Survey Section in July 1951. He was originally seconded to the Section to take part in the rabbit surveys associated with the release of the first myxomatosis-infected animals. From 1952 onwards he was able to develop his special interests in birds. He has worked on a number of Australian species, including parrots, pigeons and finches, but his chief subjects have been wild ducks and mallee fowl.

First World Meteorological Day

The wide scope of the application of meteorological knowledge to agriculture, aviation, shipping, flood protection, water resource questions of many kinds, industry and the activities of the general public is little realized. Still less are the potentialities of

warnings issued by the meteorological services of the world appreciated. These warnings are specifically designed to advise aviators, farmers, fishermen, sailors and all those whose work is affected by the weather. The World Meteorological Organization has therefore established the anniversary of the implementation of the Convention of the World Meteorological Organization, March 23, 1950, as World Meteorological Day. The first of these days was celebrated on March 23, 1961. The object is to attract world public interest to the work of the meteorological services and to the assistance they can give. It is also designed to show the need for continuous interchange of meteorological information on a world-wide basis and for meteorological collaboration in other ways, thus demonstrating that the provision of meteorological services in each country is one of the tangible results of day-to-day co-operation between nations. The 109 members of the World Meteorological Organization have been invited to celebrate the World Meteorological Day annually in their country by such means as exhibitions, lectures, visits to national forecasting offices, television and radio coverage.

Experiments on Animals

A BILL, *S*3570, providing for the control of experiments on animals, has recently been introduced in the U.S. Senate. As an aid to its sponsors the secretary-general of the Universities Federation for Animal Welfare, Major C. W. Hume, has submitted a report on the present practice in Great Britain (*Opinions of British Scientists of Home Office Control of Experiments on Animals*. Pp. 8. London: Universities Federation for Animal Welfare, 1961). The report has been based on questions addressed to British scientists who use animals in their experimental work and, with one exception, show that men of science are well content with the present system. They are satisfied that the present system of control and experiment administered by the Home Office does not in any way frustrate experimental work of the highest quality; and they wish to retain Home Office control so that persons without scientific training may not be permitted to experiment on animals without supervision.

Welfare and Care of Laboratory Animals

THE March issue of the *Bulletin of the International Committee on Laboratory Animals* is considerably bigger than some of its predecessors, because it contains, in addition to its usual international news items, a list of corresponding members, notes on the visit of the secretary-general, Dr. W. Lane-Petter, to Norway, the Near East and the U.S.S.R., and a long bibliography of papers on various aspects of research, classified according to the experimental animals used, including invertebrates. The Committee is organizing a symposium on "The Problems of Laboratory Animal Disease", which will be held in Czechoslovakia early in September. The Proceedings of the symposium on "Living Animal Material for Biological Research" have now become available. Full information about the many activities of the Laboratory Animals Centre is given in the *LAC News Letter*, published free in January and July and obtainable, as the other publications mentioned above also are, from the director, Dr. W. Lane-Petter, Laboratory Animals' Centre, Medical Research Council Laboratories, Woodmansterne Road, Carshalton, Surrey.

History of Science

THIS new annual review of literature, research and teaching in the history of science is edited by A. C. Crombie (Oxford) and M. A. Hoskin (Cambridge), and published at Cambridge by W. Heffer and Sons, Ltd. There is a board of advisory editors consisting of G. Buchdahl, Herbert Butterfield, F. N. L. Poynter and W. P. D. Wightman. The review will contain critical essays surveying recent work on special topics, and others directing attention to problems for research. There will also be sections devoted to book reviews, surveys of articles of special interest published in other journals, and information about research in progress, teaching and other matters relating to the professional development of the subject. The first number will be published early in 1962.

Queen Victoria Museum and Art Gallery, Launceston, Tasmania

THE recent issues of the *Records* and the annual reports for 1958–59 and 1959–60 of the Queen Victoria Museum and Art Gallery are complementary to each other. They indicate that museums, in addition to a policy for the conservation of objects, are also centres of scholarly research and do their share in the elucidation of scientific, historical and aesthetic problems. The reports are a record of the vigorous activity of the staff in spite of the usual lack of good exhibition and storage space. In accordance with the general policy of widening the contacts of the Museum with the public, display space has been obtained in the central shopping area of the city. This provides accommodation for a series of fortnightly exhibits of special objects as well as the display of notices regarding the activities of the main Museum. The *Records* are concerned with the geology of western and northern Tasmania and deal with both the topography and stratigraphy of the area (New Series. No. 12: Comments on the Cainozoid History of Western Tasmania. By B. Scott. Pp. 10. No. 13: Erosion Surfaces in Western Tasmania. By B. Scott. Pp. 11. Launceston: Queen Victoria Museum and Art Gallery, 1959 and 1960).

Work in the Antarctic during I.G.Y.

RUSSIAN explorers have been interested in the Antarctic since their first expedition led by F. G. Bollingshausen and M. P. Lazarev during 1819–21. During the International Geophysical Year, when the Antarctic region was studied by a combined effort of twelve nations, the Soviet expedition, centred on the settlement of Mirny, carried out considerable work in this part of the Antarctic continent. In a series of articles published in *Priroda* certain results of this work are given. Thus B. V. Dubovsky (*Priroda*, **7**, 45; 1960) provides a note on two newly discovered valleys, one called 'The Valley of I.G.Y.' and the other 'Lazarev's trough'. V. D. Novikov (*Priroda*, **8**, 43; 1960) provides an account of the construction of the scientific base Mirny, which was completed during February 1956, and later of eight additional bases. All these bases provided means of systematic and detailed geological, glaciological and meteorological studies, all of which are briefly described by Novikov. In two articles A. G. Dralkin (*Priroda*, **9**, 48; **10**, 27; 1960) describes the Soviet expedition to the South Pole in 1959 and their meeting of the American contingent of the Polar Amundsen-Scott station. The results of the study of the ice sheet and of the

Earth's crust in the Antarctic continent are presented by G. E. Lazarev and S. A. Ushakov (*Priroda*, **12**, 17; 1960). These results show that in the eastern Antarctic the average thickness of the ice sheet is not less than 2,000 m. and its maximum thickness 4,000 m. The level of the rock surface below the ice sheet varies from 1,000 m. above sea-level to 800 m. below sea-level. The thickness of the Earth's crust (above 'Moho') is 5–10 km. for the oceanic type, and 25–70 km. for the continental type. The average density of the crust is 2·8. The result of the gravity work is also discussed and it is suggested that the ice load produces a sag in the crust of the order of 600–700 m.

Singing Sand

As the result of deepening the channel of the River Dnieper below the town of Kremenchug a small artificial island of sand was formed. This sand, as described by G. G. Velikii (*Priroda*, 6, 82; 1960), when trodden on emits a singing sound. Neither very dry nor very wet sand will 'sing'. As a rule the sand emits a high pitch in the morning and a lower pitch towards the evening. The 'singing sand' from the Dnieper may thus be compared with the 'musical sand' from the Isle of Eigg in Scotland and other localities.

Rabies in India

The prevalence of rabies in India is indicated in the report of the Director of the Pasteur Institute of Southern India, Coonoor, for 1959 (Pp. i+116. Coonoor: Pasteur Institute, 1960). During the year, 34,239 courses of anti-rabies vaccine were issued. Of the 35,403 patients treated at the Institute and subsidiary treatment centres during the year, case cards were returned for 15,447 patients. Of these, 9,007 received a complete course of treatment. During the year 980 patients received a complete course of anti-rabies treatment at the Institute itself (968 Asiatics and 12 Europeans). An incomplete course of treatment was also given to 184 patients (Asiatics) of whom 52 were absolved from further treatment after the possibility of rabies in the biting animals had been excluded. One death was recorded among the 1,164 patients who received complete or incomplete courses of treatment giving a mortality-rate of 0·08 per cent. During the period 1907–59, the total number of patients treated at the Institute was 47,197, among whom 417 later died of rabies giving a mortality-rate of 0·88 per cent. Equally encouraging figures are shown by the subsidiary centres where, in 1959, the number of deaths among 8,027 patients who received a complete course of treatment had fallen to 12 (0·15 per cent). Anti-rabies treatment was also made available for the prophylactic treatment of animals. During the 37-year period from 1923 to 1959, 51,382 animals have received anti-rabies treatment, among which 473 deaths have been reported, giving a mortality-rate of 0·92 per cent. The report also describes the routine work and fundamental research into the nature of other diseases carried out at the Pasteur Institute.

Isolation of Malignolipin from Malignant Tumours

Kosaki and his co-workers isolated a new phospholipid, malignolipin, from human malignant tumours on the basis of its affinity for porphyrin, and found that it was composed of choline, spermine, phosphoric acid and fatty acid; was specific to malignant tumours; and that it promoted intraperitoneal growth of Ehrlich's ascites cancer. A large amount of malignolipin is needed to establish the structure of this compound, and to reveal its biological and, especially, pathophysiological significance. The method previously described was not suitable for extracting malignolipin in large quantities and, recently, Kosaki and his colleagues have described how the substance can be produced in considerably increased quantities (*Mie Med. J.*, **10**, No. 2; August 1960). The investigation makes clear that malignolipin is a phospholipid which has not previously been isolated. Two other articles in the same journal also deal with malignolipin. One indicates a method for detecting and measuring the substance in various tissues including blood and ascites and the other describes the column chromatographic isolation of malignolipin.

Trapping of Plasma by Red Cells

An accurate method for dividing red-blood cell columns has been devised by Peggy Clark and B. J. Walsh of the New South Wales Red Cross Blood Transfusion Service, Sydney (*Austral. J. Exp. Biol. and Med. Sci.*, **38**, Part 6; Dec. 1960). Blood is placed in polyvinyl chloride tubing which is sealed at one end with a glass bead. This tubing is inserted into a piece of glass tube before centrifugation, and later the contents can be frozen before the tubing is divided. The method was used to measure the amount of plasma trapped with the red blood cells. From these measurements the ratio of the true to the observed hæmatocrit value was found to be 0·94 at centrifugal forces greater than 1,430*g*. The ratio decreased with decreasing relative centrifugal force, but variations in the hæmatocrit value did not alter the correction factor. The amount of plasma trapped in the centrifuged and sedimented normal human blood decreased from top to bottom of the red-cell columns, but the amount in different sections of the columns became uniform as the time of centrifugation or of sedimentation increased. A blood sample with a high sedimentation-rate showed a different pattern on sedimentation.

Leverhulme Research Awards

The following fellowships and research grants tenable for periods up to two years have been announced: *Fellowships*, Dr. A. M. Dunn, lecturer in veterinary parasitology, University of Glasgow, for work on the parasitic helminth fauna of wild ruminants in Britain; P. Haggett, University demonstrator in geography, University of Cambridge, for work on secular changes in the forested area of the Serra do Mar, Brazil, 1814–1962; Dr. R. P. A. Sneeden, lecturer in chemistry, University of Glasgow, for investigations on the structures of large-ring antibiotics; Dr. L. E. Sutton, demonstrator in physical chemistry, University of Oxford, for studies on the significance of molecular shapes and sizes. *Research grants*, N. S. Angus, chief metallurgist, the Production Engineering Research Association, Melton Mowbray, for a metallurgical and chemical examination of samples of early iron and steel; E. G. Bowen, professor of geography and anthropology, University of Wales, Aberystwyth, for studies on the historical geography of the early Christian period in Celtic Europe; J. Heath, of the Nature Conservancy, Grange-over-Sands, for taxonomic and biological studies of the Micropterygidae and Eriocraniidae;

R. F. Jessup, official of the Midland Bank, Ltd., for a survey of Roman barrows in Britain and northern Europe; M. Kaufman, senior lecturer in plastics technology, National College of Rubber Technology, for his studies on the history and development of the plastics industry; W. A. Sands, senior scientific officer, H.M. Overseas Civil Service (Research Branch), for a revision of the termite subfamily Nasutitermitinae from the Ethiopian zoogeographical region; Dr. E. C. Southward, independent research worker, Marine Biological Association, Plymouth, for studies on the biology of *Pogonophora*.

Fishery Research Training Grants

THE Ministry of Agriculture, Fisheries and Food and the Department of Agriculture and Fisheries for Scotland are offering a number of one-year post-graduate training grants in fishery research tenable from October 1. These grants are intended to enable selected candidates to undergo a specified course of training to fit them for the investigation of problems in marine or freshwater science. Applications will be considered from candidates for permission to register for a higher degree in circumstances where this seems likely to be consistent with the requirements of the approved fishery research training programme. The number of training grants to be awarded during 1961 will probably not exceed three. Both men and women are eligible to apply. Candidates must be British subjects and graduates with honours in science of a university or possess equivalent qualifications. The value of the training grant will depend on the centre at which training is undertaken, and on whether the student is able to live at home, but will not normally be less than £270 nor exceed £420 per annum. For candidates with two years postgraduate experience, however, a grant of up to £470 per annum may be awarded. Further information can be obtained from the Secretary, Development Commission, 3 Dean's Yard, Westminster, London, S.W.1.

The Association of Applied Biologists

THE following honorary officers were elected for 1961–62 at the recent annual general meeting: *President*, Dr. P. W. Brian; *Vice-President*, Dr. M. A. Watson; *President-Elect*, Prof. H. G. H. Kearns; *Treasurer*, Dr. F. Raw; *General Secretary*, Dr. L. Broadbent; *Programme Secretary*, M. J. Way; *Editor*, R. W. Marsh; *Assistant Editor*, Dr. I. Thomas. New members of Council elected were: Dr. F. T. Last, F. G. H. Lupton, Dr. D. Rudd Jones and D. W. Wright.

American Society for Engineering Education

THE following have been elected officers of the American Society for Engineering Education: *President*, Dr. Robert W. Van Houten, president of the Newark College of Engineering and director of the Newark Technical School; *Vice-Presidents*, Dr. George A. Marston, dean of Engineering at the University of Massachusetts, and Dr. Curtis L. Wilson, Dean of the Missouri School of Mines and Metallurgy; *Treasurer*, Wendel W. Burton, of the Minnesota Mining and Manufacturing Co.

The International Society for Research on the Reticuloendothelial System

THE following have been elected officers and council members of the International Society for Research on the Reticuloendothelial System: *President*, Dr. Albert S. Gordon (United States); *Vice-President (Europe)*, Dr. Bernard N. Halpern (France); *Vice-President (Western Hemisphere)*, Dr. Ignacio Gonzalez-Guzman (Mexico); *Vice-President (Asia)*, Dr. Kaneyoshi Akazaki (Japan); *Secretary-Treasurer*, Dr. John H. Heller (United States); *Council*, Dr. Shigeyasu Amano (Japan), Dr. Baruj Benacerraf (United States), Dr. Charles A. Doan (United States), Dr. Thomas F. Dougherty (United States), Dr. Tede Eston (Brazil), Dr. John F. Loutit (United Kingdom), Dr. Alberto M. Marmont (Italy), Dr. A. Ashley Miles (United Kingdom), Dr. John W. Rebuck (United States), Dr. Jorge Da Silva Horta (Portugal), Dr. Bo Thorell (Sweden), and Dr. Guy Voisin (France).

The International Union of Crystallography

THE International Union of Crystallography has announced three forthcoming symposia: a symposium on "Electron and Neutron Diffraction", to be held at Kyoto, Japan, during September 25–30 (further information can be obtained from Prof. S. Miyake, Science Council of Japan, Ueno Park, Tokyo); a symposium in commemoration of the fiftieth anniversary of the discovery by Prof. Max von Laue of the diffraction of X-rays by crystals, to be held at Munich during July 25–28, 1962 (further information can be obtained from Prof. F. Bopp, Institut für Theoretische Physik der Universität, Geschw. Scholl-Platz 1, Munich 22); sixth general assembly and international congress of the Union, to be held in Rome during September 9–18, 1963 (further information can be obtained from Dr. W. H. Taylor, Crystallographic Laboratory, Cavendish Laboratory, Cambridge).

Rutherford Jubilee International Conference

A CONFERENCE is to be sponsored by the International Union of Pure and Applied Physics, the Royal Society, the Institute of Physics and the Physical Society, and the University of Manchester, to commemorate the discoveries of Rutherford at Manchester, and in particular the fiftieth anniversary of the Rutherford scattering law. The conference will be held at the Physics Department, University of Manchester, during September 4–8. The programme has been divided into nine sessions: *September* 4 (1) high-energy investigations of nuclei (morning), (2) collective motion in nuclei (afternoon); *September* 5 (3) the nuclear ground-state (morning), (4) Rutherford at Manchester (afternoon); *September* 7 (5 and 6) direct interactions (morning and afternoon); *September* 8 (7) weak interactions (morning), (8) open session (afternoon), (9) conference summary. Further information can be obtained from Dr. L. J. B. Goldfarb, Rutherford Jubilee International Conference, Physics Department, The University, Manchester, England.

University News: Belfast

DR. R. COMMON has been appointed to a lectureship in geography, and Mr. M. Cohen has been appointed to a lectureship in applied mathematics.

Birmingham

DR. W. F. VINES, university demonstrator in physics, University of Cambridge, has been appointed to a vacant established chair of physics within the Department of Physics from October 1, 1961. The title of professor of taxonomic botany has been con-

ferred on Dr. J. G. Hawkes, at present senior lecturer in taxonomy in the Department of Botany, from May 1, 1961.

The following appointments have also been announced. *Senior lectureships*: Dr. G. V. Chester (mathematical physics); Dr. A. S. Jones (chemistry); Dr. L. W. Poel (botany); Dr. J. W. Railly (mechanical engineering); Mr. J. G. Henderson (electrical engineering); Sir Francis Knowles (anatomy); Mr. A. A. Walters (econometrics and social statistics); Dr. W. E. Cavenagh (social study). *Lectureships*: Dr. D. E. Cohen (pure mathematics); Mr. H. P. Rogosinski (pure mathematics); Dr. R. H. Jones (civil engineering); Dr. M. H. Jeynes (bacteriology); W. R. H. Batty (chemistry); Dr. J. P. Simons (chemistry); Prof. E. N. Corlett (engineering production); Dr. A. J. Miller (highway and traffic engineering); T. Brereton (mining and minerals engineering); J. R. Rawling (mining and minerals engineering). *Research fellowships*: Dr. J. Lehmann, to be Imperial Chemical Industries Research Fellow in the Department of Chemistry; P. Johnson, in the Department of Medical Biochemistry and Pharmacology; R. Joy, in the Department of Medical Biochemistry and Pharmacology; Dr. B. Sakita, in the Department of Mathematical Physics.

The University has received and accepted during the period December 22, 1960–April 12 gifts and grants totalling £271,113 for research purposes. Included in this figure are: a grant of £157,143 from the Ford Foundation to support a long-term programme of research in the Department of Anatomy into the reproductive physiology of monkeys; a grant of £42,300 over five years from the Department of Scientific and Industrial Research for research on organic fluorine compounds in the Department of Chemistry.

Edinburgh

The following appointments were recently announced: *Senior Lecturers*, Dr. E. A. Smith (public health and social medicine), Dr. Allan Campbell (zoology); *Lecturers*, G. O. Goudie (engineering), Dr. Tao-Ching Hsu (engineering), A. L. Florence (engineering).

Glasgow

Dr. C. H. Wilson, vice-chancellor of the University of Leicester, has been appointed principal of the University of Glasgow, in succession to Sir Hector Hetherington, who retires on September 30.

London

Dr. W. B. Whalley, reader in organic chemistry in the University of Liverpool, has been appointed to the University chair of chemistry tenable at the School of Pharmacy.

Dr. I. C. Percival has been appointed to the University readership in applied mathematics tenable at Queen Mary College, and Dr. S. J. Pirt, principal scientific officer at the Microbiological Research Establishment, Porton, has been appointed to the University readership in microbiology tenable at Queen Elizabeth College.

Dr. P. Armitage, a member of the Statistical Research Unit of the Medical Research Council at the London School of Hygiene and Tropical Medicine, has been appointed to the University chair of medical statistics tenable at that school. Dr. Dennis Lacy, lecturer at St. Bartholomew's Hospital Medical College, has been appointed to the readership in zoology and comparative anatomy tenable at that college.

Dr. J. A. W. Dalziel of the Imperial College of Science and Technology has been appointed reader in inorganic and analytical chemistry in the Chelsea College of Science and Technology. Dr. J. D. Donaldson of the University of Aberdeen has also been appointed as a lecturer in the Department of Chemistry of the College.

Manchester

Dr. F. J. Ursell, at present lecturer in mathematics at the University of Cambridge, has been appointed Beyer professor of applied mathematics in succession to Prof. M. J. Lighthill on a date to be arranged.

Announcements

Sir John Cockcroft, master-designate of Churchill College, Cambridge, has been appointed chancellor of the Australian National University, Canberra, in succession to Lord Bruce; this appointment will not affect Sir John's position at Cambridge.

Prof. J. R. Partington has been given the Dexter Award of the American Chemical Society for his work in the history of chemistry. Prof. Partington is emeritus professor of chemistry in the University of London, but for some years has been resident in Cambridge. The Dexter Award consists of a money prize and a plaque, and it is expected that the Award will be made at a meeting of the Chemical Society in the autumn by Dr. Edelstein, president of the Dexter Chemical Corporation of New York.

Dr. G. Malcolm Dyson of Loughborough, Leicester, has been given the Austin M. Patterson Award of the American Chemical Society for his work on the storage and retrieval of scientific data by computer techniques. The award is made every two years in honour of the late Dr. Austin M. Patterson in recognition of contributions in the field of chemical literature and especially in the documentation of chemistry. This is the first time that the award has been made to a non-American.

Dr. E. Eastwood, chief of research of Marconi's Wireless Telegraph Co., Ltd., Chelmsford, Essex, has been appointed director of research responsible to the managing director for the Company's research policy.

Prof. George Temple, professor of natural philosophy, University of Oxford, has been appointed chairman of the Aeronautical Research Council, in succession to the late Prof. W. J. Duncan.

The thirteenth British Electrical Power Convention of the Electrical Development Association is to be held at the Winter Garden, Eastbourne, during June 12–15. The theme of the Convention will be "Electricity in the Prosperity and Welfare of the Nation". Further information can be obtained from J. I. Bernard, Electrical Development Association, 2 Savoy Hill, London, W.C.2.

A summer school in health physics (radiation protection) arranged by Dr. Hugh D. Evans, lecturer in radiation hazards and health physics, will be held in the Department of Chemical Engineering and Chemical Technology, Imperial College of Science and Technology, during July 3–14. Further information can be obtained from Dr. H. D. Evans, Imperial College of Science and Technology, Prince Consort Road, London, S.W.7.

THE SECOND U.K. *SCOUT* SATELLITE

THE British National Committee on Space Research, the U.K. Steering Group on Space Research and the U.S. National Aeronautics and Space Administration have agreed on the scientific instrument payload for the second U.K. *Scout* satellite to be launched by the U.S. National Aeronautics and Space Administration. The scientific instruments, as in the first British *Scout* satellite, will be designed and provided by British scientists.

The experiments are designed to measure radio emissions from the Galaxy at wave-lengths too long to penetrate the Earth's atmosphere; to measure the vertical distribution of ozone in the regions of the atmosphere in which it is being formed; and to measure the number and size of fine dust particles encountered by the satellite. In addition, the galactic radio equipment is designed to gain information on the electrical condition of the high atmosphere.

It is expected that the satellite will be launched in about two years time. The orbit will probably pass over the United Kingdom and the United States, and it should be possible to receive radio information both in these countries and at stations in the British Commonwealth.

As for the first British *Scout* satellite, this one will be launched by a four-stage rocket system using solid propellants. It is expected that the satellite orbit will range between 300 and 2,000 km. from the Earth. The instrumentation is being so arranged that the satellite will supply information on Galactic noise, atmospheric ozone and micrometeorite flux.

Galactic Noise

A project to measure the galactic noise in the frequency-range 0·75–3 Mc./s., and the exploration of the upper ionosphere, is to be carried out by Dr. F. Graham Smith, Mullard Radio Astronomy Observatory, Cavendish Laboratory, University of Cambridge.

Dr. Smith will have three objectives in mind: (*a*) to measure the intensity of the galactic background at as low a frequency as possible under known conditions of receiver sensitivity and under known conditions of ionospheric effects on propagation and aerial impedance; (*b*) to watch for temporal or spatial variations of galactic radiation; (*c*) to explore the electron density in the upper *F* region.

Atmospheric Ozone

Measurement of atmospheric ozone is under the direction of Dr. R. Frith and Dr. K. H. Stewart (Air Ministry, Meteorological Office, London). This will be carried out by two methods: (*a*) a spectrum scanning method; (*b*) a method in which a broad band of the spectrum is observed.

Dr. Frith's experiment will have as its main objective the measurement of the vertical distribution of ozone in the Earth's atmosphere as often and in as many places as possible. These measurements should add to our knowledge of the processes forming and destroying ozone, of the air motions which distribute it and of the effects of ozone on the thermal equilibrium of the upper atmosphere. Measurements will be made of the intensity of the radiation received from the Sun at selected wave-lengths in the ozone absorption region in the ultra-violet at times when the satellite is entering or leaving the Earth's shadow and the solar rays have to pass through the Earth's atmosphere to reach the satellite.

Micrometeorite Flux

The measurement of the micrometeorite flux is is being organized by Dr. R. C. Jennison (Nuffield Radio Astronomy Laboratories, University of Manchester, Jodrell Bank, Cheshire).

Dr. Jennison's experiment has as its objective the detection and measurement of micrometeorites encountered by the satellite. He will use a technique in which the holes formed in a thin metallic film by the impact of micrometeorites will be detected by an optical method. Sunlight passing through the holes will fall on a photosensitive strip of solar cells and give a signal from each hole in turn from which the number and size of the holes, and hence of the micrometeorites, can be deduced. The sensitivity is such that the holes formed by the particles, 1μ in diameter or greater, may be detected.

THE BRITISH AGRICULTURAL HISTORY SOCIETY

THE annual conference of the British Agricultural History Society was held during April 5–7 at Seale Hayne Agricultural College. On the first evening members heard papers from Mr. Peter Holmes, the County agricultural officer, and Dr. W. G. Hoskins, of Oxford. Mr. Holmes described the farming regions of Devon and did his best to disabuse his audience of the idea that Devonshire was entirely composed of the good red soils associated with the 'Glorious Devon' of the travel posters. He emphasized the importance of the hill-farming economy and explained also that there were large areas of indifferent shale soil in the north and north-east which were difficult to farm and not immensely productive.

Dr. Hoskins has recently been engaged in a study of the types of farmhouse on Dartmoor and made an appeal for more field work in the area for, as he said, "The history of the moor is as yet largely unwritten". He outlined briefly what is known of the earlier settlement of the moor and discussed its recolonization at the end of the Middle Ages. There are, he explained, still to be found many sixteenth- and seventeenth-century 'long houses' or buildings of the type that had both human dwelling and cattle stalls under one roof with a common doorway and central dividing passage.

The following day Dr. Hoskins led an excursion over the moor and showed the conference examples of

this type of house. The party also visited a deserted village site below Hounds Tor which has recently been discovered by members of the Ordnance Survey. About twelve house sites, thought to be identified with seven or eight farms, are clearly visible from the rubble remains, but nothing is yet known of the date of settlement or of desertion; excavation on the site will start this summer.

On the second evening of the conference members heard a paper from Prof. Slicher van Bath, head of the Department of Rural History at Wageningen in the Netherlands. Prof. Slicher van Bath discussed the use of farm accounts as material for investigating farm management and agricultural output between the Middle Ages and the eighteenth century. He outlined the results of a study he had made of extant accounts in several countries, including those of the English early seventeenth-century farmer, Robert Loder of Harwell (Camden Third Series, 53, 1936).

On the last morning of the conference there were papers from Mr. J. Z. Titow of Cambridge and Prof. Beresford of Leeds. Mr. Titow discussed his recent work on the types of manors to be found on the Winchester estates in the thirteenth century. It had, he said, been assumed that the descent of villein property was mainly from father to son, but he produced substantial evidence to support a plea for considering more seriously the position of widows. On many of the Winchester manors it was clear that holdings were often left to the widow and that a kind of 'widow cycle of inheritance' was thus set up. A young man in search of a holding would therefore seek a widow with one. As a result of this a widow might remarry and leave the holding on her death to her second husband who in his turn remarried, leaving it on his death to his widow who might then marry again; direct descent to the eldest son appeared to be relatively uncommon.

Prof. Beresford set out some provisional ideas on the development of the unusual settlement pattern in fourteenth-century Cornwall. He explained that a great deal more work was required on Cornish settlement patterns, and that potential workers would be encouraged to know that from the material in the Duchy of Cornwall archives it was possible to trace the occupation of Duchy holdings from the fourteenth century to the early nineteenth. Dr. Hoskins, in his concluding remarks as chairman for Prof. Beresford, said he hoped members, as a result of the conference, would be more conscious of the need for work in south-west England and the rich material that awaited them. He was glad, too, that the Society had met in the highland zone, for, in his opinion, the British highlands had been neglected by agrarian historians.

J. W. Y. Higgs

DISEASE TRANSMISSION BY TICKS

THE papers presented at the recent sixth symposium of the Zoological Society of London on "Some Aspects of Disease Transmission by Ticks", held in London on March 8, revealed how some of the pieces of this complex jig-saw puzzle are gradually being filled in, but at the same time it was indicated that there are major deficiencies in our knowledge. Dr. J. MacLeod, by reference to a very interesting mechanical analogue of the forces at work, showed that the disease associations of ticks represent meshes in the food web of a biotic community which includes the pathogens, their tick vectors, the vertebrate hosts and the vegetational environment which supports and/or shelters them all. In this connexion it is worth noting that the physical relationships of tick distribution in Britain to the type of ground-cover are known for only one of the nineteen species of ticks; the biotic relationships, with two exceptions, are practically unknown. So far as British ticks are concerned, *Ixodes ricinus* has been the species most thoroughly investigated, principally because of its known disease relations. One of these diseases, Scottish louping ill, like other viruses of tick encephalitides, appears to have a casual rather than an intimate association with its hosts, which are principally sheep in Britain. Although the ease with which this disease can be transmitted by non-British ticks, for example, *Rhipicephalus appendiculatus*, suggests that any of the mammal-infesting British ticks would be capable of transmitting it to any British mammal; the infection has been demonstrated in *I. ricinus* from sheep in Nature, both by inoculation and infection.

Clinically, louping ill resembles poliomyelitis of man, and the virus multiplies primarily outside the central nervous system and during the fever, which precedes clinical signs, the pathogenic micro-organism can be detected in the blood. Dr. W. S. Gordon's experimental results indicate that most sheep on a louping ill farm eventually become infected. Many develop only a fever, recover and are afterwards immune, but a small proportion develop clinical signs of infection of the central nervous system. In these cases lesions of an encephalomyelitis can be demonstrated and virus recovered from the brain and the spinal cord. On a world scale, according to Dr. C. E. Gordon Smith, there are thirteen known tick-borne animal viruses transmitted by five genera of hard ticks and one of soft ticks. All these viruses, except one, cause disease in man or domestic animals which are usually incidental hosts of the viruses. Their long-term natural maintenance depends on the geographical and behavioural association between vector tick and ground-frequenting mammal, and bird species, in the blood streams of which the virus inoculated by tick-bite can circulate adequately to infect further ticks. Because tick populations are adequate only where suitable vegetation provides the appropriate microclimate, infections occur in restricted foci. Wild vertebrates do not usually show the disease, but can be infected and circulate virus only once because of antibody formation, and accordingly their population turnovers must supply enough new susceptibles annually. Movement of these viruses to new areas probably depends on the carriage of infected ticks by large mammals or migrant birds. A stable enzootic disease changes to epizootic or epidemic mainly because of population-changes in ticks or vertebrates, or introductions by man of domestic animals or introduction of virus to new areas.

A second febrile disease of sheep and cattle in Britain is tick-borne fever, which was discovered during the investigation of louping ill by Gordon

et al. Hitherto tick-borne fever has been classified as a *Rickettsia*, but Dr. A. Foggie indicated that apart from the presence of an arthropod vector it has little in common with the true rickettsiae, such as those causing typhus and Rocky Mountain spotted fever. The forms seen in parasitized phagocytes have some resemblance to large viruses, and, under the phase-contrast microscope, the elementary bodies in morulæ have been seen in rapid Brownian movement, a phenomenon paralleled in colonies of psittacosis virus. While the organism had been provisionally named *Rickettsia phagocytophilia*, Dr. Foggie was of the opinion that it should now be included in the genus *Cytoecetes*, in so far as it morphologically resembles the type species *C. microti*, a tick-borne parasite of the polymorphs of voles in Massachusetts. Tick-borne fever is widespread, and an important point, made by Dr. MacLeod, was that in relation to 'inefficient' links in the biocœnose through self de-ticking, as in birds and some carnivores, transmission can occur by the second day after attachment of nymphs. Sheep are a reservoir of infection for ticks for at least several weeks after subsidence of the reaction. Cattle and goats are susceptible, and cross-infectivity and cross-immunity tests by Dr. Foggie suggest that there may be specific differences between the bovine and ovine strains of the organism; a recently isolated strain from red deer was of similar infectivity to the sheep strain. The harmful effects of louping ill are aggravated by the presence of the tick-borne fever micro-organism, as shown by Dr. Gordon's experiments in exposing susceptible sheep to natural infection with louping ill and tick-borne fever.

In the wider field of rickettsial infections and ticks, Prof. D. S. Bertram outlined the characteristics of rickettsial organisms as deduced by various workers from studies, including some by electron microscopy, on species of *Rickettsia* pathogenic to man. The significance of ticks in human tick-borne rickettsiosis was considered as well as comments on tick-borne *Rickettsia*-like organisms of veterinary interest. Prof. Bertram then illustrated that differentiation within the controversial assemblage of pathogenic and symbiotic organisms may benefit from electron microscopy, and that this technique presents an opportunity for fruitful re-examination of the fate of the different rickettsiae in their tick hosts.

Although tick pyæmia is constantly associated with an infestation of *Ixodes ricinus*, the tick does not appear to be a vector of the causal *Staphylococcus*. Dr. Foggie's observations show that *Staphylococci* of the same bacteriophage types as those found in tick pyæmia cases were found to be common commensals on the skin of lambs in both tick-free and tick-infested areas. Lambs in the neutropænic phase of tick-borne fever were shown to be a hundred-fold more susceptible to the intravenous inoculation of *Staphylococci* than healthy lambs. The subcutaneous or intradermal inoculation of *Staphylococci*, either with or without an extract of tick salivary gland, or the feeding of ticks on heavily contaminated skin areas, failed to reproduce the disease in both normal and neutropænic lambs.

Piroplasmosis (redwater fever) in cattle in Britain is due to a piroplasm now believed to be distinct from *Babesia bovis*, and for which resuscitation of the earlier name of *B. divergens* is proposed. Dr. H. E. Shortt made the point that piroplasmosis is one of the major causes of morbidity and mortality in cattle, and as such has a serious effect in limiting the potential food supplies of man. So far as is known, ticks are the chief and very likely the only vector of this condition, and, although Africa is probably the most seriously affected continent, all parts of the world harbour both piroplasms and their tick-vectors. Our knowledge of the life-history of the piroplasms in the tick is still inadequate and Dr. Shortt, in describing the life-cycle of *Babesia canis* in *Rhipicephalus*, has made notable contributions to filling in many of the blanks. The possibility of the introduction into Britain of equine and canine piroplasmosis, transmitted by *Dermacentor reticulatus* on the continent, was made by Dr. MacLeod. The suggested occurrence of *B. caballi* in Britain cannot be ignored, and with the apparent establishment of *D. reticulatus* in south-west England, due probably to similar ecological requirements to those of *I. ricinus*, the wild and free-range ponies of Devon and Cornwall, and in the New Forest, may well be ecologically susceptible to devastation by one or both of these disease agents if they were introduced. Their susceptibility is more probable from the apparent catholicity of the vector-range of these piroplasms, as the latter have been transmitted experimentally by several tick species.

Man is normally insusceptible to infection, but as ticks are almost as ubiquitous as mosquitoes and in infested regions man is constantly exposed to their bites, the possibility of the tick acting as a reservoir of occult or inapparent parasites of man cannot be ignored. Prof. P. C. C. Garnham stated in this connexion that the removal of the spleen in man abolishes immunity and the occult parasites multiply and a fatal infection may ensue. The point was made that thousands, if not millions, of people living under rural conditions, and in contact with pastures, may harbour inapparent infections of *Babesia*, other piroplasms, or even certain tick-borne viruses. Whether such a condition is harmless, even in people possessing a spleen, is a subject being investigated further by Prof. Garnham.

Relapsing fever, a tropical disease associated with soft ticks, is transmitted by the bite and/or contamination of the bite wound by the coxal fluid which is produced by some species during feeding. Dr. G. A. Walton, in discussing human relapsing fever epidemiology in Eastern Africa, described the morphological, biological and distributional peculiarities of four species of Argasid ticks previously included under the name *Ornithodoros moubata* (Murray, 1877). The part played by each of them in the transmission of human relapsing fever was outlined with reference to the evolution of the East African domestic subspecies, and the decisive effect on local transmission of *Borrelia duttoni* by the feeding preferences of its races on one hand and the distribution and social behaviour of the native human races on the other. The existence and implications of immunity to the infection in man were illustrated in relation to minor and major human population movements and to other factors producing changes in the territorial incidence of the disease. Dr. M. G. R. Varma directed attention to the fact that, in an infected tick, spirochætes may be found in practically every organ; but the organs are not necessarily infected with the same frequency or to the same degree. Moreover, two species of spirochætes may behave differently towards the same tick organ. Both the frequency and the degree of infection are connected with the method of transmission of spirochætes. Thus it has been shown

that the salivary glands of nymphs of *Ornithodoros moubata* are more heavily infected with *Borrelia duttoni* than are those of adults. There is also some evidence to show that infection of the salivary glands may die out in the course of time, so that old adults, apparently as a result of repeated feeds, rarely transmit the infection by bite.

Infection of the coxal glands in those species of ticks which do not produce any coxal fluid while feeding can have no importance in the transmission of spirochætes and such ticks transmit solely by the bite. Coxal fluid from such ticks has been shown to be non-infective although the glands themselves may be infected.

Continued experimental passage of the spirochætes through the vertebrate hosts may result in their failure to infect ticks successfully. However, by inoculating spirochætes directly into the hæmocœle, they are able to infiltrate the salivary glands and coxal glands and transmit the infection, suggesting that the gut may act as a partial barrier to the entry of spirochætes into the hæmocœle.

Some knowledge of the nature of the food imbibed by ticks and the methods of acquiring it may be of significance in assessing the timing of the intake and introduction of blood pathogens from and to the host. Examination of sections of larval and nymphal ticks feeding on rat skin by Miss Evelyn Sutton and Dr. D. R. Arthur shows evidence that a process involving the intake and digestion of non-blood tissue occurs. Moreover, field observations of adult *Ixodes ricinus* feeding on cattle revealed that ticks of the same degree of engorgement range in colour from light yellow to greyish, especially in the earlier stages. These colour differences are a reflexion of the colour of the gut contents visible through the integument, and, as afterwards confirmed by spectrophotometric analysis, the darker coloured gut contains a high proportion of blood and the lighter coloured gut a predominance of non-blood fluids. The ingestion of blood-inhabiting pathogens by the tick may accordingly be delayed for some days and in some cases may not occur at all. In certain larvæ, particularly those with short penetrant ability, it may well be that the diet is exclusively one of non-blood digested tissues, in which event the ingestion and passage of blood-inhabiting pathogens are negligible.

One of the significant features in ticks and mites is the ability of their pathogens to pass transovarially from one generation to the next. Prof. Bertram discussed how this may happen in rickettsiæ, Dr. Varma showed how it occurred in ticks infected with *Borrelia duttoni* and Col. Shortt mentioned the passage of *B. canis* through the ovum of *Rhipicephalus*. Transovarian transmission in ticks and mites may be either obligatory or incidental. Prof. Garnham stated that obligate transovarial transmission occurs in *Karyolysus* and in *Rickettsia tsutsumagushi*, whereas *B. canis* for example, as Shortt described, may either progress from adult to egg to larva (that is, transovarial) or from stage to stage. Viruses sometimes pass through the egg, and spirochætes often are transmitted in this way, although the organism tends to become less virulent to the vertebrate host after such passage, and, if this is repeated for several generations, the progeny is eventually freed of infection. It has been suggested that ease of transovarial transmission in ticks may be related to the fact that only a single membrane separates the egg from the hæmocœle, whereas in insects greater insulation against the entry of viruses and pathogens is afforded by the presence of three membranes.

The proceedings of the symposium will be published in full by the Zoological Society of London.

D. R. Arthur

QUEEN ELIZABETH COLLEGE, LONDON

SIR JOHN ATKINS LABORATORIES

QUEEN ELIZABETH COLLEGE (University of London) was again honoured by a visit from H.M. Queen Elizabeth, the Queen Mother, Chancellor of the University of London, when, on May 9, she opened the new building on Campden Hill, the Sir John Atkins Laboratories. Her Majesty addressed members of the College and distinguished guests assembled outside the Laboratories, and then made a tour of the building, where she talked to a number of the staff and students who work there.

The building, designed by Messrs. Adams, Holden and Pearson, and erected by Messrs. Holland and Hannen and Cubitts (G.B.), Ltd., is six storeys of brown Buckinghamshire facing bricks, with panels of cream bricks between the lines of windows, and reconstructed Portland stone dressings. It houses the Departments of Biology, Microbiology, and Nutrition, which moved from the main College building last autumn, and released much-needed space there for the expansion of other departments. On part of the top floor there is a self-contained Isotope Unit for the use of any department needing to work with radioactive materials.

The Nutrition Department was founded in 1954, following the establishment by the University of London of the degree of B.Sc. (Nutrition), still the only degree of its kind in the world. For the first six years it worked in very restricted quarters, in part of two prefabricated huts. Now it has an area of more than 12,000 sq. ft., and is the first university department in Britain to have been specially designed for teaching of and research in nutrition. In addition to a large laboratory for forty-two undergraduates and a smaller teaching laboratory for twelve advanced students, there is accommodation for twenty-two research workers, with ten animal rooms for the rats and mice used in studying nutritional problems. Already, with the aid of grants from the research councils, from research foundations and from various industrial organizations, it has been possible to add eight graduate research workers to the staff of the Department. From this beginning the College will go on advancing by research the science of nutrition, a science which has assumed a new importance in face of the imminent danger of food production and food distribution failing to keep pace

with the upsurge of world population; and by training a steadily increasing body of nutritionists, qualified in all the aspects of the subject—scientific, social and economic—which now make up the full study of nutrition, the College will provide the workers needed not only to help in the fight against hunger and malnutrition, but also to deal with the different nutritional problems of the well-fed countries.

The Department of Microbiology, already known for its research, but hitherto greatly hampered by lack of space, now has fully air-conditioned research laboratories and is probably one of the best equipped non-medical microbiology departments in any university in Britain. At present its undergraduate teaching is confined to ancillary courses, but if the University decides to introduce a B.Sc. (Special) degree in microbiology, Queen Elizabeth College will be among the first to provide courses for it. The large teaching laboratory, with about forty student places, is admirably fitted for the purpose. The University has just instituted a readership in microbiology tenable at the College, and from October 1961 the reader will be head of the Department.

The Department of Biology has the whole of the ground and first floors and part of the lower ground floor of the new building for zoological and botanical teaching and research. In its old premises it had little room for research workers. Now it has accommodation for twenty, including the teaching staff, and already six postgraduate research workers have been added to the Department, including one post-doctoral Research Fellow. The two teaching laboratories each have sixty places for undergraduates, and the College, which already had one of the biggest entries in the University for the B.Sc. (General) degree, hopes to be able to increase the number still further. Britain needs specialists, but it also needs many scientists with a broad and balanced education for industry, for teaching, and for many other important walks of life. This need is well filled by graduates with a London B.Sc. (General) degree, and the College aims at seeing that this degree is accorded the importance it deserves.

It is most fitting that this new building should be named after Sir John Atkins, the first Fellow of the College. Sir John was largely responsible for the foundation of the College. As a young doctor he felt so strongly the need for a college where domestic subjects could be taught with a proper scientific background that in 1911, by his own efforts, he raised the necessary funds for the erection of the main buildings in Campden Hill Road. He joined the Governing Body in 1912 and still serves on it. Through all these years he has watched over the interests of the College, and cherished its aims. For thirty-six years, as chairman of the Council, he guided it through the most crucial stages of its development. The Sir John Atkins Laboratories will be a permanent reminder of all that past, present and future generations of students owe to him.

DAMAGE BY *RHIZINA UNDULATA* IN CONIFEROUS PLANTATIONS

THOSE who attempt to establish, or re-establish, forests artificially on land on which there was never any natural forest, or from which every remnant of a natural forest soil has long since disappeared, are always liable to encounter fresh trouble. This fact is brought home forcibly in a recent publication by the Forestry Commission which is concerned with a fungous disease which, significantly, has been observed to be serious mainly in plantations recently established on non-forest soils*.

The title, *Group Dying of Conifers*, is unfortunate. Groups of trees may die for a variety of reasons as, for example, from strikes by lightning, from deposition of toxic materials, like manure heaps, within the stand, from attacks by fungi other than *Rhizina*, and so on, and why this forest record is not simply entitled *Rhizina undulata* with an appropriate equivalent in English is misleading and difficult to understand. A suitable name would appear to be the 'fire-site fungus'.

Rhizina undulata Fr. ex Fr. is described as 'colonizing' the sites of fires lit during forestry operations in pole-sized stands. From these sites it spreads outwards over a limited period of years, with the result that groups of dead trees occur within the stand. In some cases these breaks in the canopy give access to strong winds and form starting points of what may develop into serious windthrow. *Rhizina* has been recognized as a parasite since 1894, and has been described from both eastern and western States in the United States as well as from Europe. Significantly, it does not appear to attack leaf-tree species, only conifers. The first record of so-called 'group-dying' in Great Britain seems to have been in 1936, but it is only since 1953 that *Rhizina* has been frequently observed associated with groups of dead trees in the British Isles.

Messrs. Murray and Young, on the basis of a study of dead groups of trees in 58 forests or estates in Britain, 50 of which are situated along the western seaboard, have clearly confirmed that the fungus becomes recognizable on fire sites, and a very large proportion of the dead groups were associated with fires. This has led to the prohibition of all fires, even those lit for the brewing of tea, in or near the plantations of the Forestry Commission. This means of control can be strongly recommended to other forest owners, although it is often difficult to overcome the passion for tidiness which seems normally to be associated with artificial plantations.

The general history of the disease and its behaviour are described together with a more detailed survey of two infested forest areas in Scotland. There is an excellent description of the fungus itself; but in discussing the nature of the attacks and the behaviour of the fungus the authors have obviously been handicapped by inadequate experience of site examination and by the prevailing ignorance of soil organisms, including fungi, and of their relationship

* Forestry Commission. Forest Record No. 46: *Group Dying of Conifers*. By J. S. Murray and C. W. T. Young. Pp. 19 + 12 figures. (London: H.M.S.O., 1961.) 3s. net.

to the organic matter in the soil. It is unfortunate that no full description of any of the sites or soils examined is published although it may have been recorded elsewhere. It has been found that Sitka spruce is especially susceptible to attack, and not solely because it happens to occur in no fewer than 38 of the 58 areas examined. A point which is not made clear is whether *Rhizina* exists in the soil before the plantation is established—possibly associated with the organic matter therein—and Sitka spruce is most often planted on soils with a high content of organic matter or on grass- or rush-covered sites. *Rhizina* may exist in close association with grasses, for example, and only when the organic matter is altered or consumed by fire does it virulently attack the feeding roots of the trees. What, for example, happens when *Rhizina* encounters the mycorrhizal fungi usually associated with conifers? There is a great need for more research into the occurrence and behaviour of all the micro-organisms found in the soil, and it is important for foresters that soil research should be based, where possible, on the soil of the natural forest. While the natural forest is a reality which has stood the test of time, the artificial forest still remains an illusory concept nowhere brought to satisfactory permanency, and liable to be seriously disturbed by organisms, like *Rhizina*, beyond the forester's control.

TRENDS IN JUVENILE DELINQUENCY

FOR some years the World Health Organization has taken an interest in the problem of juvenile delinquency. In 1949, at the request of the United Nations, the Organization carried out a study of the psychiatric aspects of the origin, prevention and treatment of juvenile delinquency as a contribution to the United Nations programme for the prevention of crime and treatment of offenders. Since then, representatives of the World Health Organization have taken part in many conferences and have regularly attended meetings of the United Nations Consultative Group on the Prevention of Crime and the Treatment of Offenders; and the Organization has, through its Regional Office for Europe in Copenhagen, organized a seminar on the psychiatric treatment of offenders.

In 1959, again at the request of the United Nations, another study was carried out by a psychiatric consultant, Dr. T. C. N. Gibbens, senior lecturer in forensic psychiatry in the University of London, who was appointed by the World Health Organization to complement the earlier study with a review of present trends in juvenile delinquency, based on his own personal experience, the recent literature and first-hand information obtained during visits to a number of countries—Australia, Denmark, the Federal Republic of Germany, Israel, Lebanon, Poland, Sweden and Yugoslavia. Dr. Gibbens's report, which was submitted to the second United Nations Congress on the Prevention of Crime and Treatment of Offenders, has now been published with some minor amendments*.

The new forms or manifestations of juvenile delinquency consist partly of delinquent acts which are a consequence of new opportunities for crime, but which do not differ in their essential character from more traditional forms, and partly of offences which appear to reveal a fundamental change in behaviour, or the participation of sections of the community which have not previously been involved in crime.

It is with these newer forms that the author is primarily concerned in his review of social changes, changes in family life and in the individual delinquent, special property offences, sexual offences, wayward girls, violent offences, alcoholism and drug addiction, and hooliganism. He also discusses present trends in prevention, paying particular attention to the development of prediction studies designed to identify young children who are in danger of being seriously delinquent in the future, and to the tendency to design preventive programmes in such a way that their results can be scientifically evaluated. A chapter on treatment deals with diagnosis, treatment at liberty and institutional treatment.

* World Health Organization Public Health Papers, No. 5: Trends in Juvenile Delinquency. By T. C. N. Gibbens. Pp. 56. 2 Swiss francs; 3s. 6d.; 0.60 dollar. (Geneva: World Health Organization; London: H.M.S.O., 1961).

SIMIAN MALARIA

A RECENT issue of the *World Health Organization Chronicle* is concerned with the transmission of malaria parasites between monkey and man*.

The knowledge that such a transmission can take place dates back to 1932, when, in India, Knowles and Das Gupta found that *Plasmodium knowlesi* could cause a febrile infection in man. Knowledge of simian malaria in relation to man was extended in 1948, when *P. rodhaini* of African chimpanzees was found to be morphologically and immunologically identical with *P. malariae* of man. Subsequent work showed that human malaria parasites such as *P. vivax*, *P. falciparum* and *P. ovale* could be transmitted to chimpanzees through anopheline mosquitoes although patent parasitæmia appeared only in splenectomized apes.

In certain parts of West Africa the chimpanzee is known to harbour *P. malariae*, and man has been shown to be readily susceptible to the strains harboured. The anopheline vector of the *P. malariae* of these chimpanzees has not been identified. In Sarawak certain strains of human parasites of quartan malaria have been observed to have a peculiar morphology which suggested that the parasite might be of simian origin. In the Amazon region of South America, some *P. vivax* infections in man have been held to be derived from simian malaria. *P. simium*, found in howler monkeys of the forests near Santos, has been suspected of being closely related to *P. ovale*.

* *World Health Organization Chronicle*, **15**, No. 1, January 1961.

In May 1960, came a new development. During research at the U.S. National Institutes of Health, Bethesda, by Eyles, Coatney and Getz on the transmission to rhesus monkeys of *P. cynomolgi bastianelli*, some very large-scale inoculations of sporozoites into monkeys were carried out. Two staff members of the Institutes, neither of whom had had any recent contact with human malaria, were dealing at close quarters with heavily infected mosquitoes; they both developed illness with fever which, after a remittent period, proved to have tertian periodicity. Blood smears, made on new slides and stained with new stain in clean dishes, showed that both had *vivax*-type parasites with enlarged erythrocytes and Schuffner's stippling. Five millilitres of blood from each of the two individuals, injected intravenously into two uninfected rhesus monkeys, produced *cynomolgi*-type infections in 8 days in one monkey and in 10 days in the other. Two human volunteers each received 10 ml. of blood intravenously from one of the individuals; both developed clinical attacks of malaria with *vivax*-type parasites, enlarged erythrocytes, and Schuffner's stippling, but without high parasite densities.

The two individuals in whom the infection was first discovered received chloroquine treatment within 24 hr. of diagnosis. At the time of treatment both showed low levels of parasitæmia. The parasites promptly disappeared with treatment and no relapse occurred.

Another person allowed 30–50 *Anopheles freeborni*, heavily infected with *P. cynomolgi bastianelli*, to feed on him, and experienced headache, malaise and fever eleven and twelve days later. No parasites were found in his blood, but a monkey free of disease, intravenously injected with 10 ml. of his blood, developed an overt infection in 6 days. A fourth person developed a typical malaria paroxysm with *vivax*-type parasites fourteen days after being bitten by 10 *A. freeborni*, heavily infected with *P. cynomolgi bastianelli*.

Cross-immunity studies were undertaken at Bethesda on two monkeys which had recovered spontaneously from infections with *P. cynomolgi bastianelli*. On being re-inoculated with heavy doses of parasites taken from one of the two monkeys which had been infected by intravenous injection of the blood of one of the two accidentally infected staff members, one monkey showed a transient parasitæmia indicating almost complete immunity. The other had an attack of malaria that was shorter and less severe than the usual *bastianelli* attack. These results supported the view that the human infections were due to *P. cynomolgi bastianelli*.

The significance of these infections of human beings lies in the fact that they were transmitted by mosquitoes which had fed on rhesus monkeys. The theoretical possibility of natural infection of man with monkey malaria had already been suspected; but it was the anthropoid ape, not the monkey, which was formerly suspected as being a possible carrier of human malaria. Monkeys are much more numerous and widespread than apes, and live in closer association with man, and at least seven species of anophelines are known to be able to transmit *P. cynomolgi* to rhesus monkeys. Some of these species are exophilic, and therefore unlikely to be affected by residual insecticides; moreover, the host preferences of anopheline vectors for man and for the monkey are often almost the same. Consequently, experimental proof that man can be infected by monkey malaria opens up a new range of possibilities.

EFFECT OF MASS TRANSFER ON THE VELOCITY OF RISE OF BUBBLES IN WATER

By Dr. J. H. LEONARD and Prof. G. HOUGHTON

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ALTHOUGH Datta, Napier and Newitt[1] were the first to suggest that "mass transfer (from bubbles) may be accompanied by some retarding effect", no definite conclusions were reached in this respect from their experiments on carbon dioxide bubbles rising in water. In the present measurements both velocities of rise and mass transfer-rates for bubbles could be measured separately over short distances in a column of water. The apparatus used was a modification of that[2] in which soluble bubbles were formed in a cup under mercury and allowed to rise up through a completely closed 'Pyrex' glass column (9 cm. internal diameter, 270 cm. long) filled with water; the change in volume of each bubble was recorded by registering the position of a mercury meniscus in a horizontal capillary side-arm, which provided the only opening to the atmosphere. By stretching a fine platinum wire through the capillary and connecting the wire to a bridge circuit it was possible to record the position of the mercury meniscus and hence the bubble volume on one channel of a high-speed Sanborn oscillograph. Although the principle was used earlier[3,4], these earlier experimenters used high-speed photography to determine the volume of the bubble by photographing the position of the liquid meniscus in the capillary. However, the present apparatus also differs from that of Houghton *et al.*[4] in that the rising bubbles interrupt a series of light beams and photoelectric cells placed at intervals of 47·0 cm. up the column. As the bubble passed each light beam, the change in light intensity was recorded on a second channel of the Sanborn oscillograph. In this way it was possible to determine the average bubble velocity and the average mass transfer-rate separately over each 47·0-cm. section of the column together with the corresponding average bubble diameter over the same section. In certain instances the velocities of rise, obtained by the method described, were also confirmed independently in a separate apparatus by forming the bubbles at jets of various sizes, using a micrometer hypodermic syringe, and then timing them over a 110 cm. length of column, using a stop-watch and starting the measurements at a distance of 20 cm. from the jet (cf. ref. 5).

Figs. 1 and 2 show that mass transfer has a profound effect on the velocity of rise of soluble gases in water for bubbles with equivalent spherical diameters

in the range 2–6 mm. Bubbles with diameters greater than 7 mm. have not been included in these figures, since mass transfer was found to have no significant effect on the velocities of rise of bubbles in the diameter range 6–20 mm., presumably because the profile drag and inertial effects present in the larger bubbles were much more important than the surface effects. The mass transfer rates for the gases in Figs. 1 and 2 are in the following descending order: carbon dioxide > nitrous oxide > ethylene ≃ nitrous oxide – nitrogen mixture (50 mole per cent) > nitrogen. The largest velocities of rise are found for insoluble gases represented in Fig. 1 by the data for nitrogen bubbles rising in water saturated with nitrogen; in this system, the bubbles expand as they rise, because of the reduction in the hydrostatic head. The gas with the largest mass transfer rate is carbon dioxide, which also demonstrates the lowest velocities of rise. The systems with intermediate mass transfer-rates between insoluble nitrogen and carbon dioxide also show intermediate effects on the velocity of rise. For example, Figs. 1 and 2 show that bubbles formed from a 50–50 mixture of nitrous oxide and nitrogen have velocities of rise half-way between those of pure nitrogen and pure nitrous oxide. In fact, the figures show that the effect of mass transfer is to lower the velocity of rise as the mass transfer-rate increases, so that the velocities of rise are in the following order: nitrogen > nitrous oxide – nitrogen mixture (50 mole per cent) ≃ ethylene > nitrous oxide > carbon dioxide.

It is evident that the lowering of the velocity of rise for soluble bubbles cannot be explained simply on the basis of a change in terminal velocity of rise with diameter, since the velocities of rise of insoluble bubbles decrease with increase in diameter in the range 2–6 mm., whereas, when mass transfer occurs, the velocity either increases or does not change much with diameter. Furthermore, in no case did the diameter change more than 5 per cent of its value over any section of the column.

Another possible explanation might be that as a bubble decreases in size, it should accelerate if the velocity of rise follows the curve for insoluble bubbles.

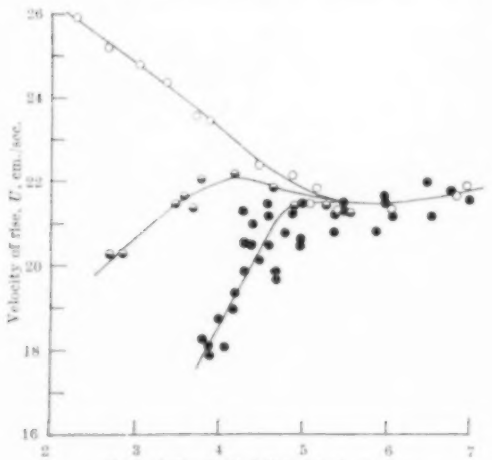

Fig. 1. Effect of mass transfer on velocity of rise of bubbles in water

●, carbon dioxide bubbles in water; ◒, ethylene bubbles in water; ○, nitrogen bubbles in nitrogen-saturated water

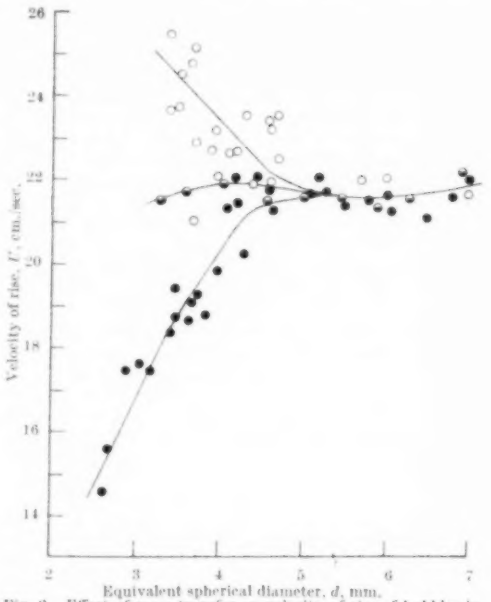

Fig. 2. Effect of mass transfer on velocity of rise of bubbles in water

●, nitrous oxide bubbles in water; ◒, nitrous oxide–nitrogen bubbles (50 mole per cent nitrous oxide) in water; ○, nitrous oxide bubbles in aqueous nitric acid (*p*H 0·7)

The acceleration would then produce an increase in virtual mass of the bubble (cf. ref. 6), which in turn would reduce the buoyancy forces and indirectly affect the velocity of rise. However, the experiments using pure nitrous oxide bubbles in aqueous nitric acid (*p*H 0·7) shown in Fig. 2 tend to eliminate this explanation. The velocities of rise of pure nitrous oxide bubbles in dilute nitric acid were the same as the velocities of rise of insoluble nitrogen bubbles, even though the mass transfer-rate of nitrous oxide in the nitric acid solution was the same as that in pure water. This observation indicates that, although the phenomenon depends on the mass transfer-rate, it is also sensitive to the presence of electrolytes in solution. A simple explanation for all these phenomena that comes to mind is that electrokinetic effects caused by mass transfer might induce an electrically charged layer at the bubble surface, which in turn would retard the bubble motion by increasing the skin friction. This surface potential would be analogous to the zeta-potential, which is known to be sensitive to the presence of acids and alkalis, so that the presence of a zeta-potential would also explain the apparently anomalous case of nitrous oxide bubbles in aqueous nitric acid as well as the dependence of the phenomenon on the rate of mass transfer across the boundary. Furthermore, electrokinetic effects at the surface would explain why the phenomenon is only observed with small bubbles, where the surface effects would be large and inertial and profile effects would be small.

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SCHULZE–HARDY RULE AND MASS ACTION LAW

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IN two previous papers of this series[1,2] the equation:

$$''c(1-x)/'cx = 10^{('z-''z)a} = {}'D/''D = S \quad (1)$$

was shown to be valid for the equilibrium concentrations $''c$ and $'c$ and for the adsorbed fractions, x and $1-x$ of two ions of valency $''z$ and $'z$ in equilibrium with the coagulated silver iodide. a is a constant, S the selectivity coefficient, $''D = x\gamma/''c$ and $'D = (1-x)\gamma/'c$ are their distribution coefficients.

Equation (1) can formally be obtained from the difference of the equations:

$$\log {}'c = -{}'za + \log(1-x)\gamma - \log {}^{0}D \quad (2)$$

and

$$\log {}''c = -{}''za + \log x\gamma - \log {}^{0}D \quad (3)$$

resp.

$$\log {}^{0}D = \log {}^{i}D - {}^{i}za \quad (4)$$

where $\gamma = \bar{C}\, w/V$ is the maximal adsorbed amount expressed in equivalents per litre, w the amount of the solid in the system of volume V, $\bar{C}$ is the adsorbing capacity of the solid, that is, the amount adsorbed per unit amount of the solid, and ${}^{0}D$ is the distribution coefficient of a hypothetical particle of zero valency which would be adsorbed as charged particles.

The exchange of adsorbed counter ions can be represented by association processes between counter ions and the adsorbed potential determining ions:

$$(A_{i_z}M_{z^{-1}})_{\text{ads.}} \rightleftharpoons ({}^{i}z\ A^{z-})_{\text{ads.}} + z^{-}M^{i}$$

If chemical thermodynamics is applied to these association reactions the constants in equations (1) to (4) are obtained:

$$a/0{\cdot}4343 = \mu_{A^{z^-}_{\text{ads.}}}/z^{-}RT$$

$$\ln {}^{0}D = (\mu^{0}_{AM^{i}})_{\text{ads.}}/z^{-} - \mu^{0}_{M^{i}})/RT$$

$$\ln {}'D = \ln a_{AM'}/a_{M'} = \ln(1-x)\gamma/c'$$

$$\ln {}''D = \ln a_{AM''}/a_{M''} = \ln x\gamma/c''$$

$$\ln {}^{i}D = \ln a_{AM^{i}}/a_{M^{i}}$$

for

$$z^{-} = 1,\ a_{AM'} = (1-x)\gamma,\ a_{AM''} = x\gamma,$$

$a_{M'} = {}'c, a_{M''} = {}''c$. $\mu_{A^{z^-}_{\text{ads.}}}$ is the chemical potential of the potential determining ion in the double layer. The constancy of a with pI for different z, was established experimentally, therefore $\mu_{A^{z^-}_{\text{ads.}}}$ is constant and independent of pI, while the adsorbed quantity of the potential determining ion is inversely proportional to pI (refs. 1–3). $\mu^{0}_{M'} = \mu^{0}_{M''}$ and $\mu^{0}_{AM'} = \mu^{0}_{AM''}$ are the standard chemical potentials of the counter ions M' and M'' of valency $'z$ and $''z$ in the solution and in the adsorbed layer and $a_{M'}$, $a_{M''}$ $a_{AM'}$ and $a_{AM''}$ are their activities.

By eliminating a in equations (2), (3) and (4) the following equation is obtained:

$$K_c = {}^{0}D^{('z-''z)} = {}'D^{''z}/''D^{'z} = [(1-x)\gamma/'c]^{''z}(''c/x\gamma)^{'z} \quad (5)$$

which is identical with the mass action law equation, K_c being its constant.

If $'c \gg ''c + \gamma x$, then $x \ll 1$ and $1-x \doteq 1$ and equation (5) can be written:

$$\log 1/''D = {}''z/'z \log {}'c - {}''z/'z \log \gamma K_c^{-1/'z} \quad (6)$$

Equation (6) is identical with Strickland's expression[4] suggested for the determination of ion charges and was used by Kraus and Nelson[5] and others[6] for this purpose.

Consequently, the coagulated silver iodide may be considered as an ideal ion exchanger, the role of the coagulating ions being that of the exchange ions.

Supposing that two ions are exchanging in accordance with coulombic repulsion forces, one of valency $'z = 0$, the other of $''z = z$, then equation (1) may be written as:

$$\log c/{}^{0}c = -az + \log x/(1-x) \quad (7)$$

The logarithm of the concentration at which a given constant ratio of two ions is adsorbed (x = constant) is increasing linearly with the decreasing valency of the ion. ${}^{0}c$ can be considered as a concentration of a hypothetical adsorbable species without charge, which follows from equation (7) for known x, z and c.

It is a general opinion that the Schulze–Hardy rule should be a consequence of the relative adsorption tendencies of the coagulating counter ions of different valencies. The coagulation value $c_{\text{coag.}}$ is an experimentally observed limiting concentration at which the coagulation sets in abruptly, and all terms determining it must be constant. The positions which are in the double layer of the coagulated silver iodide occupied by coagulating counter ions have to be occupied on the stable silver iodide by stabilizing particles. In a simple system like the system AgI—I^{-}—H_2O—counter ion, the only particles which can be considered as stabilizing are the water molecules. The adsorbed quantity of remaining species, the I^{-} ions, does not depend on the concentration of the counter ions and cannot be made responsible for coagulation. The coagulation will be induced when the stabilizing water molecules are exchanged by the coagulating counter ions. The reactions representing this process in the double layer can be written:

$$(A_zM_{z^-})_{\text{ads.}} \rightleftharpoons z\ A^{z-}{}_{\text{ads.}} + z^{-}M$$

$$(A_{z^-}.z^{-}H_2O)_{\text{ads.}} \rightleftharpoons 2\ A^{z-}{}_{\text{ads.}} + z^{-}H_2O$$

Chemical thermodynamics applied to these association reactions gives the equation (3) for $z^{-} = 1$ with equal constants, a and ${}^{0}D$, namely:

$$\log c_{\text{coag.}} = -za + \log x_{\text{coag.}}\gamma/{}^{0}D \quad (8)$$

for:

$$a = (\mu_{(A_{z^-}z^{-}H_2O)_{\text{ads.}}}/z^{-} - \mu_{H_2O})0{\cdot}4343/2RT = \mu_{A^{z^-}_{\text{ads.}}}\ .\ 0{\cdot}4343/z{\cdot}RT$$

$$\ln {}^{0}D = (\mu^{0}_{(AM)}{}_{\text{ads.}} - \mu^{0}_{M})/RT$$

$\mu_{(A_z^{z-}.xH_2O)_{\text{ads.}}}$ is the chemical potential of the hydrated potential-determining ion in the double layer. It is constant because both $\mu_{A_{\text{ads.}}^{z-}}$ and μ_{H_2O}, the chemical potential of water in the liquid phase, are constant. ^{0} stands for the respective standard chemical potentials. Equation (8) should represent the Schulze–Hardy rule and is according to the adsorption theory, thermodynamically justified. Any other non-linear (log $c_{\text{coag.}} - z$) relationship would contradict the requirements of thermodynamics.

A linear relation between the logarithm of coagulation value and valency was deduced theoretically by Težak[7,8] and was confirmed experimentally[7,9]. On the basis of this linear relationship, Težak *et al.*[9,10] suggested a coagulation value method for the determination of ion charges.

It was shown experimentally[1,2] that the slope of the Schulze–Hardy line in equation (8) and the slope of the adsorption line for $x/(1-x)$ = constant in equation (7), namely, the a values, are equal for the negative silver iodide system. Consequently, Strickland's and Težak's methods can be considered as the consequence of the same adsorption-desorption, respectively, ion exchange equilibria for which the mass action law is valid. The equality of a is thermodynamically justified, since a is proportional to the chemical potential of the adsorbed potential determining ions, which is the same in both cases.

If the coagulation value represents that activity of the coagulating ion in solution at which, in the double layer, its chemical potential becomes equal to the chemical potential of the stabilizing particles, then $x_{\text{coag.}} = 0{\cdot}5$.

Since ^{0}D cannot be determined by adsorption experiments on coagulated silver iodide (for $c > c(x = 1)$ ^{0}D is not constant) it follows from coagulation experiments:

$$\log {}^{0}D \doteq -za + \log 0{\cdot}5\,\gamma/c_{\text{coag.}}$$

I wish to express my thanks to Prof. Božo Težak for his interest in my work and for many helpful discussions.

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PHOTOCHEMICAL REACTIONS IN FROZEN SOLUTIONS

By Prof. SHIH YI WANG

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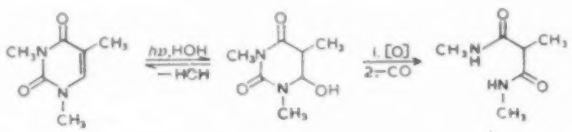
SZENT-GYORGYI has shown that photochemical reactions in aqueous solutions, in frozen aqueous solutions and in frozen aqueous solutions containing organic solvents differ from each other[1]. He has recently suggested[2] that a photochemical reaction in frozen solution differs from that in liquid solution because the formation of crystalline ice forces the solute molecules into solid aggregates[3]. In confirmation of this hypothesis, he found that the phosphorescence observed in frozen solution also occurs in a dry film. Similarly, I have obtained chemical evidence that an identical photoproduct was isolated from the irradiation of pyrimidines, either in frozen solutions or as dry solid films. However, the photoproduct obtained from the irradiation of aqueous solution was different.

By extending the hypothesis of molecular aggregate formation in frozen solution, one would expect that the photochemical behaviour of a solute in frozen aqueous solution containing organic solvent would be similar to that of its organic solution; for on freezing, the organic solvent and solute molecules would be excluded from the water crystals and form 'puddles'. That the photochemical reaction actually occurs in such 'puddles' of organic solvent has been adduced from the fact that the methanolic addition product of 1,3-dimethyluracil is formed from the irradiation of 1,3-dimethyluracil either in frozen solution containing 2 per cent methanol or methanolic solution.

From this work, two novel techniques of great interest for photochemical study are evident: (1) frozen solution irradiation may be used as an efficient method for irradiating solids; (2) formation of 'puddles' may offer a new means for study of low-temperature photochemical reactions.

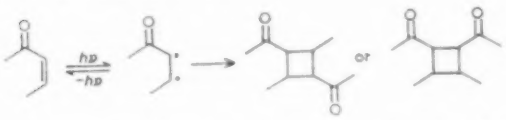
In an earlier report from this laboratory on the effect of ultra-violet irradiation on 1,3-dimethylthymine (DMT) in aqueous solution, it was suggested that a water addition product is the first intermediate formed. The intermediate is probably unstable at room temperature and reconverted to its starting material by dehydration[4]. It is not unreasonable to expect that this intermediate would become stable at low temperatures and could be isolated. In order to prove the above, an examination of low-temperature irradiation was initiated.



In frozen solution, the absorption maximum of DMT decreased rapidly when irradiated with ultra-violet light. This is to be expected if the hydration product were formed. The original spectrum would then be reconstituted by standing at room temperature. However, the product obtained from frozen

solution irradiation was stable even when treated with acid, base or heat. It must be concluded that the assumed product, 6-hydroxy-1,3-dimethylhydrothymine, was not formed. This observation indicated that irradiation with ultra-violet light in aqueous solution and in frozen solution must proceed through two different mechanisms. In order to eliminate the possibility that temperature played a part in the alteration of reaction pathways, the irradiation of DMT was carried out in the aqueous solution and in the frozen solution, both at ~0°. Since this difference in irradiation behaviour still was observed, it can be concluded that temperature alone is not the cause of the difference.

In order to further our understanding of the nature of frozen solution irradiation, the isolation and identification of the product were carried out. From the elementary analysis and molecular weight determinations, the product was readily recognized to be a dimer of DMT[5].



Photodimerization has been widely observed for α,β-unsaturated keto-derivatives[6]. These dimers are generally believed to be formed through the union of the double bonds from two molecules. A diradical intermediate, as shown, is generally favoured as the mechanism for the formation of the cyclobutyl ring. The probability of dimer formation will depend on the distance between the two reacting molecules. Therefore, photodimerizations occur mostly in the solid state rather than in solution. Since highly strained cyclobutyl rings are formed in this process, the photoproducts are known to be quite unstable. It is reported that photodimers are reconverted to their monomers by treatment with either acid[7] or heat[8] or ultra-violet light[9]. DMT-dimer obtained in frozen solution irradiation, as noted above, is stable toward heat, acid or base, but ultra-violet light converted it to the monomer, DMT, in liquid solution.

Since the DMT-dimer is formed by the irradiation of frozen solution, irradiation of frozen solution must resemble irradiation of solid aggregates. Further evidence for this assumption will be presented in the ensuing sections.

(A) Nature of Irradiation of Frozen Solutions

(1) *Heterogeneity of Frozen Aqueous Solutions.* The heterogeneity which serves as the basis for the hypothesis that solid aggregates are formed on freezing aqueous solutions is analysed quantitatively as follows: Frozen solutions of DMT and 1,3-dimethyluracil (DMU) were analysed spectrophotometrically;

Table 1

Layer*	Dry-ice mixture		Liq. N_2	Ice-NaCl	Freezer
	DMT	DMU	DMT	DMU	DMT
Outermost	$0{\cdot}66 \times 10^5$	0·42	0·74	0·49	0·21
Intermediate	1·08	1·10	1·04	1·04	0·82
Core	1·12	1·16	0·96	1·15	1·78

* When a beaker containing solution is frozen, crystals of ice will form first on the surface of the beaker and grow towards the centre. However, when such a beaker is placed instead in a tray, which in turn is placed directly on the metal shelf in a refrigerator, the top layer freezes first. Therefore, the reverse effect was observed (Table 2).

they showed differences in their concentrations between different layers. Optical density readings for a 0·1 m*M* solution after freezing are given in Table 1.

The concentration difference is often 8–10 times between two layers for compounds such as uridine, thymidine, etc.

After irradiation the frozen solutions were also analysed as three separate layers. For example, a thymine solution (0·1 m*M*, $\varepsilon^{H_2O}_{max.}$ $0{\cdot}78 \times 10^3$), gave the readings presented in Table 2.

Table 2

Layer	$\varepsilon^{H_2O}_{max.}$		Yields (per cent)	
	Before irrad.	After irrad.	Relative	Absolute
Outermost	1·53	0·19	169	88
Intermediate	0·70	0·10	76	86
Core	0·17	0·02	19	88

The relative percentage yields of dimer were calculated assuming homogeneous distribution of solute while the absolute yields were calculated on the basis of the real concentration in each layer. The relative percentage yields were found to be variable. However, when the percentage yields were calculated according to the concentration of each layer, that is, the absolute amount of material present in each layer, then the absolute percentage yields were almost the same throughout. This result suggests that the irradiation is related to the absolute amount of material present.

(2) *Effect of Temperature and Methods of Freezing on Irradiation Reaction.* When individual solutions were frozen under different conditions such as in a 'deep-freeze', or by means of liquid nitrogen or carbon dioxide-2-*n*-butoxyethanol, and then irradiated at identical temperatures in a carbon dioxide-2-*n*-butoxyethanol mixture bath, the results obtained were approximately the same. In addition, when all solutions were frozen in a dry-ice mixture but the irradiation temperature of each solution was varied by means of liquid nitrogen, carbon dioxide mixture or ice-sodium chloride baths, the decrease in absorption maximum was still the same (Table 3).

Table 3

Effect of method of freezing (DMU)

$O.D.^{H_2O}_{max.}$	In ice-NaCl	In CO_2 mixture	In liquid N_2
Before irradiation	0·973	0·965	0·960
After irradiation	0·703	0·683	0·706

Effect of temperature during irradiation (DMT)

$O.D.^{H_2O}_{max.}$	− 10°	− 70°	− 190°
Before irradiation	0·838	0·838	0·840
After irradiation	0·390	0·394	0·419

Therefore, neither the temperature during irradiation nor methods of freezing altered the photochemical behaviour of solid aggregates in frozen solutions.

One attempt was made to form a homogeneous frozen solution by dropwise freezing with dry-ice mixture. Each individual drop was added after the previous drop was completely frozen; nevertheless, dimers were formed on irradiation. These findings suggest that within the means of common laboratory facilities, heterogeneity always results when an aqueous solution is frozen.

(3) *Irradiation in Rigid Medium*[10]. In order to demonstrate that no dimerization should occur in the absence of molecular aggregates, glycerol was used as the solvent for the irradiation study. On cooling,

the glycerol solution of DMT became rigid glass rather than crystalline and the individual molecules were on the average 100 Å. apart[10]. On irradiation, the absorption maximum of DMT remained the same as before irradiation, indicating strongly that no photodimerization occurs in a homogeneous solution.

(4) *Formation of Dimers in Frozen Aqueous Solutions and Films of Dry Solid.* (*a*) Irradiation in frozen solution[11–13]. Under my experimental conditions, all the uracil and thymine derivatives tested form photodimers. Therefore, this is a general phenomenon for pyrimidine molecules which have α,β-unsaturated ketone as their predominant electronic configuration. Table 4 gives some of the compounds which have been irradiated as frozen solutions. Also given is the maximum percentage decrease at $\lambda_{max.}$ for each compound and its time for reaching this maximum decrease. Based on these two values, the quantum yields were calculated. The light energy absorbed by the solution is $1{\cdot}24 \times 10^{-6}$ Einstein per minute under this condition.

Table 4

0·1 m*M* solution	Maximum decrease in $\lambda_{max.}$ (per cent)	Minimum time (min.)	Quantum yield* × 10^{-6} (mole/Einstein)
Thymine	86	3	230
1,3-DMT	75	6	100
Thymidine	49	100	4·0
Ca^{++}-thymidylate	41	120	2·8
Uracil	68	10	55
1,3-DMU	25	15	13
Uridine	21	90	1·9
Uridylic acid	40	150	2·2
6-Methyluracil	60	80	6·0
1,3,6-Trimethyluracil	50	45	9·0

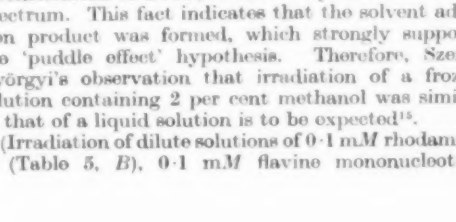
* These values are provided to indicate the order of magnitude of the quantum efficiency of the reactions. The fact that some of the light is reflected from crystalline ice surfaces renders it difficult to assign a 'true' value of light-energy absorbed by the frozen solution.

Evidence for the formation of dimers is based on the isolation and characterization of uracil-dimer (anal. found C, 42·61; H, 3·29; N, 25·16. No absorption maximum between 220–360 mμ), DMT-dimers (Isomer-I: m.p. 258–259°; mol. wt. found 301; anal. found C, 54·56; H, 6·61; N, 18·34. Isomer-II: m.p. 225–226°; mol. wt. found 302; anal. found C, 54·67; H, 6·73; N, 18·28), and thymine-dimer[13] (anal. found, C, 47·47; H, 4·69; N, 22·23. No absorption maximum between 220–360 mμ). Other photodimers were shown by the decrease of their absorption maxima during irradiation with ultra-violet light in frozen solutions. After thawing, the original spectra could be reconstituted by the irradiation of the thawed solution with ultra-violet light at *p*H ~2 (acid *p*H used to prevent the formation of the water addition product during the irradiation of aqueous solution whenever necessary).

(*b*) Irradiation of dry solid films. The question still remains, Does dimerization occur because the solute is present in dry aggregates in a frozen solution, as suggested above, or is there some more subtle reason? If only dry aggregates are required then irradiation of a dry solid film should yield similar results. When a thin layer of solid thymine or uracil was irradiated, thymine-dimer or uracil-dimer was isolated from these irradiation studies; these dimers were characterized by ultra-violet and infra-red spectra, and were found to be identical to those obtained when frozen solutions were irradiated. Not only do the foregoing results support the proposed concept, but they also emphasize that the crystalline structure of water is not necessary for the photochemical behaviour noted for frozen solution. Frozen solution irradiation offers a novel method of solid irradiation which is experimentally advantageous; it is convenient, controllable, involves neither the tedious technique nor the large quantities that are ordinarily necessary for chemical studies of irradiation reactions using dry solid.

(*B*) Photochemistry in 'Puddles'

Szent-Györgyi showed that the photochemical behaviour of a compound irradiated in a frozen aqueous solution is altered when the frozen solution contains 2 per cent methanol. He stated " . . . an admixture of 10 per cent glycerol or 2 per cent methanol to the water deprive it of its specific action on excitation because these admixtures destroyed the regularity of the water crystals"[14]. In my frozen-solution experiments, when thymine and DMT were irradiated in the presence of 2 per cent methanol or 10 per cent glycerol, the spectra were the same before and after irradiation, a finding strongly indicating that no reaction has occurred. However, since heterogeneity of the frozen solution was shown to be responsible for the photodimerization, a 'puddle effect', again based on heterogeneity, is proposed to explain the above phenomena. One may hypothesize that, on freezing, the water molecules tend to crystallize, but the solute molecules, together with some of the added methanol or glycerol, are excluded from the water to form puddles. However, 'glycerol puddles' are different from 'methanol puddles'. As noted above, the former when frozen form a rigid medium, and as a result no photodimerization should occur on irradiation. The latter when frozen form a methanolic solution, and therefore a photochemical reaction in this solution should be observed. In order to show the 'puddle effect' of methanol, a compound that fulfils the following criteria must be studied: (*a*) forms a photodimer when irradiated in frozen solution; (*b*) forms a solvent addition product when it is irradiated in solution. A compound with the above characteristics was found in DMU. When DMU dissolved in methanol is irradiated with ultra-violet light, the decreasing absorption maximum of DMU indicates the formation of 6-methoxy-1,3-dimethylhydrouracil



The addition of acid or alkali will cause 6-OCH_3 compound to revert to DMU[15]. When a frozen aqueous solution of DMU containing 2 per cent methanol was irradiated, a decrease in absorption maximum was also observed. Again, addition of acid (*p*H ~2) or alkali (*p*H ~12) caused a total reconstitution to DMU, as shown by the ultra-violet spectrum. This fact indicates that the solvent addition product was formed, which strongly supports the 'puddle effect' hypothesis. Therefore, Szent-Györgyi's observation that irradiation of a frozen solution containing 2 per cent methanol was similar to that of a liquid solution is to be expected[15].

(Irradiation of dilute solutions of 0·1 m*M* rhodamine *B* (Table 5, *B*), 0·1 m*M* flavine mononucleotide

Table 5

State	*B*	FMN	Mixture
Liquid solution	Orange	Yellowish green	Orange
Frozen solution	No light emission	Orange	Bright pink
Frozen solution + 2 per cent MeOH	Orange	Yellowish green	Orange
solid film	No light emission	Orange	Bright pink

(FMN) and a mixture of 0·1 m*M* rhodamine *B* and 1 m*M* thiamine hydrochloride were used by Szent-Györgyi to demonstrate the dramatic changes in fluorescent colours between the frozen solutions and their liquid counterparts[1]. I have extended these experiments by the comparison of these fluorescent colour changes with solid films. These were prepared by drying 10 m*M* methanolic solutions of *B*, 10 m*M* methanolic solution of the mixture and a saturated methanolic solution of FMN on glass plates. Table 5 shows the changes in colour viewed under an ultra-violet lamp (Mineralight No. *R*. 51, Ultraviolet Prod. Co., San Gabriel, Calif.). The light emission from liquid solutions and frozen solutions with 2 per cent methanol is the same, suggesting that the 'puddle' formation probably occurs in the latter. The light emission from solid films is the same as that of their frozen solutions, suggesting that the fluorescent colours observed with frozen solutions probably is due to the formation of solid aggregates on freezing.)

This 'puddle' formation in frozen solution certainly merits further investigation. This system resembles the non-aqueous environments of living organisms which permit the occurrence of specific reactions, such as electron transport in mitochondria[15] and oxygen exchange in haemoglobin[16]. By replacing 2 per cent methanol with various organic solvents, one may experiment with the molecular rearrangements, Diels–Alder reaction, etc., of various compounds. The formation of 'puddles' produces an essentially water-free medium at low temperatures for the reactions under investigation, a condition impractical to achieve by merely cooling organic solvents because of water condensation. It is my belief that this 'puddle effect' probably offers a new area for photochemical study.

At the outset of my systematic study of the photochemistry of nucleic acids and related compounds, I considered that photochemical changes occurring in the solid-state may possibly be related to the irradiation-induced changes of deoxyribonucleic acid (DNA) in biological systems. This concept is based on the Watson and Crick[17] and Wilkins *et al.*[18] proposal for the molecular structure of DNA. They suggested that DNA may consist of two polynucleotide chains helically wrapped around each other with 10 base residues per turn. The pitch is 34·6 Å. and the distance between the two layers of base residues is 3·4 Å. Thus, the proximity of the bases may permit the interaction of two adjacent base residues on the same chain to form pyrimidine-pyrimidine, purine-purine or pyrimidine-purine dimers coincident with the breaking of interchain H-bonds. The conditions for the irradiation of solid films, discussed above, for the yield of pyrimidine-dimers were obtained only after an understanding of the nature of the irradiation of frozen solutions was attained. Therefore, if biological systems and compounds such as chloroplasts, proteins and nucleic acids are closely related to the 'pseudocrystalline' state, the irradiation of solids or frozen solutions may yield more important information than irradiation in other media.

Irradiator. A bank of seven ultra-violet lamps (General Electric Germicidal tube *G*15*T*8) was used. The distance between the lights and the solution for irradiation was 33 cm. A voltage regulator was connected to the irradiator and a light intensity of 50 MW./sq. ft. was obtained[19]. For isolation study, the voltage regulator was omitted and a light intensity of 80 MW./sq. ft. was used.

Quantum Determination. This was measured by the method of Forbes and Heidt[20].

Frozen Solutions. Ten ml. of solution in a 50-ml. beaker was frozen by various means and the thickness of the solution was about 1 cm.

Separation of Layers. Fifteen ml. of frozen solution in a 100-ml. beaker was used (1 cm. thickness). It was thawed gradually by placing the beaker in a water bath at room temperature. Some of the thawed liquid was pipetted out until 5 ml. could be obtained. This was referred to as the outermost layer. Then, with further thawing, a second 5 ml. portion, the intermediate layer, was collected. The remainder was called the core layer.

Gross Irradiation for Isolation. One litre of 1 m*M* solution was frozen and then was irradiated in an enamel pan (11·5 × 18 in.) for 30 min. This pan was placed on a dry-ice mixture to keep the bath frozen. The irradiated solution was then thawed and was evaporated to dryness with a flash evaporator for further purification. Usually, the product of several runs was combined.

(*a*) *Uracil-dimer, thymine-dimer.* The crystalline residue was taken up in boiling water. After filtration, the filtrate was concentrated for crystallization. The crystalline product was obtained easily because the dimers are much more insoluble in water than the monomers.

(*b*) *DMT-dimers.* The crystalline residue was taken up in chloroform, and, after filtration, the combined solution from 3 pans was concentrated to 5 ml. To this an adequate volume, 25 ml., of petroleum ether (30–60°) was added to make the solution just appear cloudy. On standing, a crystalline product was obtained, m.p. 210–230°. Every 100 mgm. of the above product was dissolved in 2 ml. of chloroform and then 5 ml. of petroleum ether was added for crystallization. From this 45 mgm. of a product, m.p. 250–255° was obtained. Further crystallization of this product gave a high melting isomer, m.p. 258–259°. From the crystallization of the mother liquor, a low melting isomer, m.p. 225–226°, was obtained.

Irradiation of Solid Film. A 10-m*M* methanolic solution of thymine or uracil was prepared, and 5 ml. of this solution was pipetted on to a 'Pyrex' baking pan (9 × 12 cm.) very slowly and allowed to form an even, dry film over the bottom of the pan. After irradiation for 30 min., the residue was taken up in boiling water and then concentrated for crystallization.

(*a*) *Thymine.* A total of 5 mgm. of thymine-dimer was obtained by combining 5 runs. (*b*) *Uracil.* A total of 7 mgm. of uracil-dimer was obtained by combining 8 runs.

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MECHANISM OF SODIUM TRANSPORT IN CELLULAR MEMBRANES

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THE function of a nerve cell in the process of conducting impulses can easily be described by the behaviour of its membrane potential. At rest, the potential difference, outside minus inside, is about +50 to +100 mV. During activity, when an impulse passes, this potential is rapidly abolished and even to some extent reversed. Afterwards, and within a few milliseconds, the original potential difference is re-established. The wave of changes in potential is termed the action potential.

It has been shown very convincingly that the first, decreasing phase of the action potential is due to the sudden and very rapid transfer of sodium ions from the outside to the inside of the cell membrane[1]. This movement of sodium ions occurs in the direction of the concentration gradient, and thus needs no additional source of energy. The rising phase of the wave is due to an outward movement of potassium, which is again in the direction of the concentration gradient. Ultimately, the repetition of this event would lead to the destruction of the ionic concentration gradients, and thus to the loss of the ability to form an action potential, or in other words, to a block in the excitability and function of the nerve cell. However, the nerve cell membrane possesses a mechanism which is capable of transporting sodium ions from the inside to the outside, against the concentration gradient[1]. Thus this gradient does not disappear, but is eventually re-established to its full extent.

When one tries to understand the basic principles of these processes, two things have first of all to be explained: (1) the ability of the cell membrane to bring about and to maintain the concentration differences of ions on its two sides; (2) the nature of the changes which occur in the membrane permitting sodium ions to enter the cell and thus cause the action potential. As regards the first problem, it must be borne in mind that the different concentrations of sodium ions on the two sides of the membrane are in a dynamic equilibrium. There is a continuous exchange of sodium ions through the membrane, but at rest the concentrations remain constantly the same[1]. The outward movement of sodium ions is dependent on an active transfer mechanism which needs metabolic energy for its function. This energy is supplied in the form of adenosine triphosphate[1], which is in turn generated through the process of oxidative phosphorylation.

The second problem, that of the mechanism of formation of the action potential, is concerned with a sudden increase in the inward movement of sodium ions. The nature of the changes in the membrane which cause this phenomenon is still quite obscure. The discussion which follows is concerned with the mechanism of active transport of sodium ions across the cell membrane. Some new data on the nature of the biochemical mechanism underlying the phenomenon of active transport will also be presented and discussed.

Microsomal Adenosine Triphosphatase as an Indicator of Sodium Transport

Recently, evidence[2-7] has been obtained which bears on the mechanism of sodium transport across the cell membrane. This evidence also provides a plausible explanation for the mode of action of general narcotics such as ethyl alcohol[5] and ether. Some implications concerning present thought on biochemical phenomena in highly organized subcellular structures are also evident.

Microsomes from rat brain, when isolated in the manner described in detail elsewhere[3], exhibit a powerful adenosine triphosphatase activity. This activity is completely dependent on magnesium ions, and shows the property of being stimulated by sodium ions (Table 1). When sodium is present in concentrations of between 30 and 100 mM, there is observed an activity of adenosine triphosphatase of some 20–25 per cent higher than the activity in the absence of sodium. Somewhat lower concentrations of sodium show a lower stimulation, and concentrations less than 5 mM do not stimulate to a measurable extent. To find an explanation for these observations, attention is directed to the well-known phenomenon of respiratory control in electron-transport-coupled phosphorylation, catalysed by mitochondria. When phosphate and phosphate acceptors are absent, no electron transport occurs. In the brain microsomal system, less dephosphorylation of adenosine triphosphate occurs in the absence of sodium. On the basis of these experiments, it is assumed that microsomes from rat brain catalyse two enzymatic reactions, one of which has adenosine triphosphate as a substrate, the other sodium ions. These two reactions would be coupled to each other in an obligatory manner,

just as are electron transport and phosphorylation in the mitochondrial system. When no sodium ions are present, no reaction could occur with adenosine triphosphate, and a control mechanism analogous to the mechanism of respiratory control would therefore be in operation. Obviously the reaction with sodium cannot occur in a sodium-free medium, and the consequence is a lower rate of adenosine triphosphate dephosphorylation. The fact that the latter activity is not completely extinguished in the absence of sodium is capable of explanation when one considers that the microsomes may have suffered damage during the preparation, and that such damage is likely to produce a certain amount of 'uncoupling'. It is also possible that enough sodium is bound to the microsomes to cause the observed rate in the absence of sodium.

Table 1. Activity of Adenosine Triphosphatase of Rat Brain Microsomes in the Presence and in the Absence of Sodium and Potassium Ions[a]

Exp. No.	Additions	μmoles P_i liberated	Activ. (+) inhib. (−)
1	None	0·63	—
	Na^+, 0·1 *M*	0·74	+ 0·11
	Na^+, 0·01 *M*	0·65	+ 0·02
2	None	0·44	—
	Na^+, 0·1 *M*	0·57	+ 0·13
	Na^+, 0·015 *M*	0·54	+ 0·10
	K^+, 0·1 *M*	0·43	− 0·01
	K^+, 0·015 *M*	0·44	0
	Na^+, 0·05 *M* and K^+, 0·05 *M*	0·57	+ 0·13

[a] The assay contained: 20 m*M tris*-chloride buffer, *p*H 7·5, 5 m*M* magnesium chloride, 5 m*M tris*-adenosine triphosphate, 0·1 ml. of enzyme suspension in isotonic sucrose, the indicated amounts of the alkali metal ions as chlorides, and when these would not make the mixture isotonic, the necessary amount of sucrose. Final volume 1 ml., temperature 30° C., incubation time 10 min.

In this connexion, it is interesting to note that potassium ions cannot cause a stimulation in the microsomal adenosine triphosphatase (Table 1). The view has been adopted that the isolated microsomal system represents and contains the sodium-specific mechanism for the transport of ions across cellular membranes. Some evidence from other laboratories can be taken as supporting this view. Some years ago, Skou demonstrated[6] that submicroscopic particles from crab nerve possess a sodium-and-potassium dependent adenosine triphosphatase activity. He also interpreted this as an expression of an active sodium transport mechanism in these particles. Skou's results indicated that the sodium-dependent mechanism was also dependent on small amounts of potassium ions, a finding which is at variance with the results obtained in this work[2,3]. It is quite possible that the microsomal preparation contained enough potassium to mask any existing effects of this ion, and the discrepancy between the findings of Skou[6] and those of this work[3] may therefore not be important. Quite recently, Post *et al.*[7] reported on a sodium-and-potassium dependent adenosine triphosphatase in erythrocyte membrane fragments which very much resembles the enzyme from crab nerves[6] and from brain microsomes[3]. Hanzon and Toschi[8] showed that the microsomes obtained in the fractionation of brain homogenates were derived from membranous structures in the cytoplasm, the endoplasmic reticulum or the α-cytomembranes. These are probably continuous with the outer cell membrane, and probably structurally and functionally identical with it. In addition, Toschi found[9] that the acetylcholinesterase was concentrated in the microsomal fraction, thus suggesting an important functional role for this fraction in the impulse-cycle. On different lines, Hokin and Hokin[10] have postulated a mechanism for sodium transport across cellular membranes. Their views are based on the mechanism for the incorporation of phosphate into phosphatidic acids of brain microsomes. The phosphatidic acids would function as sodium carriers in the internal lipide phase of the cell membrane. The overall process results in a hydrolysis of adenosine triphosphate.

Table 2. Inhibition of Activity of Adenosine Triphosphatase by Pyridine Aldoxime Dodecyliodide[a]

Exp. No.	Additions	μmoles P_i liberated			
		in absence of Na^+	Act. (+), inh. (−)	in presence of 0·1 *M* Na^+	Act. (+), inh. (−)
1	None	0·75	—	0·93	+ 0·18
	PAD, 10^{-4} *M*	0·47	− 0·28	0·47	− 0·46
	PAD, 10^{-4} *M* and Eserine 10^{-4} *M*	0·49	− 0·26	0·49	− 0·44
	Eserine 10^{-4} *M*	0·81	+ 0·06	0·94	+ 0·01
2	None	0·72	—	0·85	+ 0·13
	PAD, 3×10^{-5} *M*	0·71	− 0·01	0·72	− 0·13

[a] The assay conditions were as in Table 1.

Note added in proof. More recent experiments have shown that the stimulation of the microsomal ATPase by sodium ions can be considerably increased by the presence of small amounts of potassium. Nevertheless, potassium alone has no effect. These findings abolish the main discrepancy between Skou's work[6] and mine.

Inhibition of the Adenosine Triphosphatase

The behaviour of the sodium-dependent microsomal adenosine triphosphatase was also studied in the presence of some substances which are known to cause a depolarization of the cell membrane, and which are accordingly of interest in connexion with the problem of active sodium transport and impulse formation. Acetylcholine showed no effect on the adenosine triphosphatase activity, either alone or in the presence of eserine, which would inhibit the acetylcholinesterase. On the other hand, the quaternary nitrogen compound pyridine aldoxime dodecyliodide (PAD) strongly inhibited the activity of adenosine triphosphatase (Table 2). The inhibition showed different characteristics in the absence and in the presence of sodium. If a suitable concentration of about 3×10^{-5} *M* was chosen, only the sodium-stimulated adenosine triphosphatase was inhibited, and the remaining activity still exceeded that obtained in the absence of sodium; the unstimulated activity was not affected at all. If the concentration of PAD was increased, the inhibition also became noticeable in the sodium-free experiments. In each case where the inhibitor concentration was sufficiently high to cause inhibition in the sodium-free experiments, the remaining activity was the same, irrespective of the presence or absence of sodium. Such behaviour suggests that the reaction is sub-maximal in absence of sodium and that PAD specifically inhibits an enzymatic reaction which is involved in the splitting of ATP. As will be seen later, another type of inhibition of the adenosine triphosphatase can also be obtained.

Dettbarn *et al.*[11,12] have shown that PAD depolarizes the nerve cell membrane. They assume that the depolarizing action of PAD is due to the fact that this substance is analogous to acetylcholine in

structure. It has indeed been shown[13] that its action on acetylcholinesterase can be explained on the basis of this molecular analogy. The foregoing experiments show that PAD inhibits the microsomal adenosine triphosphatase in a specific manner, suggesting that PAD directly interferes with the mechanism of reaction. According to the views of Nachmansohn *et al.*[14], this would mean that acetylcholine should also cause a similar inhibition. The fact that this is not so is perhaps not too serious an obstacle, if the lipide insolubility of acetylcholine is taken into account. A more serious obstacle, however, is the fact that eserine does not block the inhibition by PAD. In Dettbarn's experiments[12], eserine blocked the effect of PAD, and this effect is one of the main points in his argument for an analogy between PAD and acetylcholine.

Grundfest[15] has suggested that the inhibition of the mechanism of sodium transport is a cause of the action potential. However, such a mechanism does not seem to be sufficient to explain the great speed of the inward sodium flow during the action potential. It has been pointed out by Katz[16] and by Hodgkin and Keynes[1], that a mere inhibition of the active transport mechanism would not provide a quantitatively satisfactory basis for this phenomenon. However, as the experiments described here suggest that the active mechanism of sodium extrusion from the cell is inhibited by acetylcholine analogues, the role of this substance in the formation of the action potential in a manner closely related to that suggested by Grundfest cannot be ruled out completely.

Non-Specific Inhibitions

In addition to PAD, a number of other substances cause a decrease in the rate of hydrolysis of adenosine triphosphate by brain microsomes. Detergents, alcohols, and the anaesthetics ether and chloroform are such substances. The type of inhibition acquired with these compounds is quite different from that obtained by PAD. While the behaviour of the adenosine triphosphatase in the presence of PAD suggested a specific mode of action for this compound, no such specificity seems to be involved in the case of the other substances. Thus the same concentration of an inhibitor, for example, deoxycholate, causes about the same amount of inhibition, irrespective of whether sodium is present or not. The remaining activity is thus always, within certain limits of inhibitor concentration, higher in the presence of sodium than in its absence. It is of particular interest that dodecylsulphate, a detergent with the same lipophilic alkyl group as PAD, also causes this type of non-specific inhibition (Table 3). The role of the dodecyl group as the inhibitory principle in PAD can thus be ruled out, and the quaternary nitrogen assumes a dominant position as the active grouping in this compound. The

Table 3. Inhibition of Adenosine Triphosphatase by Sodium Dodecyl-Sulphate (DS)*

Additions	μmoles P_i liberated			
	in absence of Na^+	Act. (+), inh. (−)	in presence of 1·0 *M* Na^+	Act. (+), inh. (−)
None	0·75	–	0·93	+ 0·18
DS 10^{-4} *M*	0·59	− 0·16	0·72	− 0·21

The conditions were as described in Table 1.

Table 4. The Effect of Ethyl Ether and Chloroform on the Microsomal Adenosine Triphosphatase

Additions	μmoles P_i liberated			
	in absence of Na^+	Act. (+), inh. (−)	in presence of 0·1 *M* Na^+	Act. (+), inh. (−)
None	0·73	–	0·81	+ 0·08
Ether 0·02 *M*	0·68	− 0·05	0·75	− 0·06
Ether 0·04 *M*	0·66	− 0·07	0·73	− 0·08
Chloroform 0·01 *M*	0·62	− 0·11	0·70	− 0·11

The conditions were as described in Table 1.

analogy between PAD and acetylcholine is thus strengthened, and support is given to the possibility of an inhibition of the sodium transport mechanism by acetylcholine.

It is interesting to note that in addition to the above-mentioned detergents, compounds such as alcohols, ether and chloroform cause a non-specific inhibition of the microsomal adenosine triphosphatase (Table 4). The concentrations of these compounds used in the experiments are approximately such as would occur during heavy alcohol intoxication or during anaesthesia. The effects observed with these substances offer a new and interesting possibility of explaining their mechanism of action on a biochemical basis. First, it is known that ethanol causes a decrease in the resting membrane potential of the nerve cell[17]. Secondly, the rate of adenosine triphosphate hydrolysis is diminished by ethanol[3]. This leads to a smaller quantity of adenosine diphosphate being formed, and thus, through the well-known mechanism of respiratory control in mitochondria, to a decrease in the rate of oxygen consumption. This is in very close agreement with findings on the effect of ethanol on the oxygen consumption of the whole brain or brain slices[18]. The biochemical mechanism of the action of alcohol and of anaesthetics thus seems now to be within the reach of studies on a subcellular level.

Mechanism of the Non-Specific Inhibition

It was explained above that the inhibition by PAD of the sodium-dependent adenosine triphosphatase seems to be due to a specific inhibition of the adenosine triphosphatase reaction. The inhibition caused by the other substances mentioned above is of another type, and could not be interpreted as an inhibition in the classical manner. The mechanism of this inhibition therefore remains to be explained. All the substances tested are lipophilic in character, and would have a considerable affinity for the lipide structures forming the major part of the microsomal mass. A certain structural disorganization undoubtedly follows when these structures are exposed to detergents. In mitochondria, such phenomena have been observed and subjected to thorough study. In the present case, it is not possible to delineate the exact mechanism of the inhibition. More extensive data are needed for a complete explanation. One possibility could be that the substances mentioned bring about a disturbance in the spatial arrangement of the enzymes involved, and thus a decreased reaction-rate.

Conclusion

The study of phenomena related to the active, energy-consuming transport of molecules across

cellular membranes has generally been possible only with preparations consisting essentially of intact cells. Such a situation is not ideal for a detailed biochemical analysis of the phenomenon. A number of extremely important cell functions are intimately connected with the active transport of various substances across the cell membrane. The secretory mechanisms of glands, the re-absorption of a great number of substances in kidney tubuli, and the electrical activity of nerves and other conducting tissues may be mentioned. From the biochemical point of view all these phenomena are almost entirely unexplained. The possibility of studying phenomena related to the active transport of sodium ions through the nerve cell membrane by the use of a suspension of isolated microsomes from the brain has been indicated above. Such a technique may prove useful in the study of the mechanisms involved in these processes.

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CODING RATIO FOR THE RIBONUCLEIC ACID VIRUSES

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IT is a generally held view that nucleic acids carry the information necessary to specify the primary structure of proteins. As there are only four kinds of nucleotides in any one kind of nucleic acid and 18–20 kinds of amino-acids in protein, it is reasonable that at least a triplet of nucleotides is required to specify a particular amino-acid[1]. Several hypotheses have been advanced to account for the coding of protein primary structure in terms of nucleotide triplets[2,3]. A nucleotide triplet is presumed to be composed of adjacent nucleotides along a single polynucleotide chain (at least in the case of ribonucleic acid (RNA)).

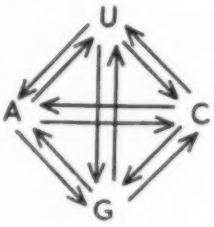
Yčas, however, has recently advanced the interesting hypothesis that, in the case of virus RNA, not a triplet of nucleotides along the RNA chain but rather a single nucleotide corresponds to any given amino-acid. This hypothesis necessitates that the 18–20 amino-acids fall into four groups, one group for each kind of nucleotide[4]. Further, in order to distinguish among amino-acids within any one group, it is necessary to invoke a second source of information not contained in the RNA of the virus (at least in the above sense of coding). This hypothesis, if true, should presumably hold for more than RNA viruses. We might expect to find a coding ratio, n (defined as the number of nucleotides specifying an amino-acid) of unity for most RNA molecules. It is the purpose of the present article to discuss Yčas's novel and important suggestion.

First, let us briefly outline Yčas's approach in arriving at the conclusion that n is unity. This approach is to compare both the protein and nucleic acid composition of six well-characterized RNA viruses, southern bean mosaic (SBM), tomato bushy stunt (TBS), cucumber (CV), tobacco mosaic (TMV), turnip yellow (TY) and polio (PV). To do this the quantity $1/2\Sigma|D_a|$ is defined as "one-half the sum of the absolute values of the differences between the quantities, expressed as moles per cent, of corresponding amino-acids in two proteins". An analogous expression, $1/2\Sigma|D_n|$, is defined for the two corresponding virus RNA's. The ratio of these two, $1/2\Sigma|D_n| \,/\, 1/2\Sigma|D_a|$, is designated r. This and the coding radio, n, are considered for the case of 'non-overlapping' codes only. The author then suggests that in general $r \leqslant 1/n$. However, this conclusion rests on several assumptions, mentioned below.

By comparing the composition of each of the RNA viruses in turn to that of turnip yellow (which has the most extreme compositional differences of all six viruses), Yčas finds the ratio r to be 0·90, SBM; 0·75, TBS; 0·66, CV; 0·83, TMV; and 1·09, PV. Two of these figures, at least, are indistinguishable from unity, and all are greater than 0·6. These high values of r are taken to mean, then, that the coding radio, n, cannot be greater than unity itself, as $r \leqslant 1/n$. Yčas shows it is possible to assign the individual amino-acids to four groups such that for all viruses the sum of the mole fractions of the amino-acids in any group is equal to the mole fraction of a particular nucleotide in the corresponding RNA, in keeping with a coding ratio $n = 1$. The nucleotide groupings are these: adenylate – glutamic acid (glutamine), glycine, leucine, phenylalanine and tryptophan; cytidylate – cysteine, lysine, methionine, proline and threonine; guanylate – alanine, arginine, tyrosine and valine; uridylate – aspartic acid (asparagine), isoleucine, histidine and serine. Unknown, X, factors not carried on the RNA distinguish among members of the same group.

Assuming a coding ratio $n = 1$, let us see what effect transformation of one nucleotide into another, or one group of nucleotides into another, has on the ratio r. For this purpose define the nucleotides as

A, C, G and U, and the corresponding amino-acids as $a_1, a_2, \ldots, c_1, c_2, \ldots$ ... There are in all twelve possible kinds of single transformations among nucleotides, when transforming (formally) the composition of one virus into that of another. These are symbolized by the diagram:



All these taken singly have an r value of unity. However, we can distinguish several types of pairs of nucleotide transformations, some of the overall r value of which is less than unity. For example,

$$\begin{matrix} A \to C \\ a_1 \to c_1 \end{matrix} \text{ and } \begin{matrix} C \to A \\ c_1 \to a_1 \end{matrix} \qquad (1)$$

this cannot be distinguished from no transformation at all, so all such pairs are eliminated from the diagram as contributing nothing:

$$\begin{matrix} A \to C \\ a_1 \to c_1 \end{matrix} \text{ and } \begin{matrix} C \to A \\ c_2 \to a_2 \end{matrix} \qquad (2)$$

this has an overall value $r = 0$;

$$\begin{matrix} A \to G \\ a_1 \to g_1 \end{matrix} \text{ and } \begin{matrix} G \to C \\ g_1 \to c_1 \end{matrix} \qquad (3)$$

this is identical with $\begin{matrix} A \to C \\ a_1 \to c_1 \end{matrix}$, and $r = 1$;

$$\begin{matrix} A \to G \\ a_1 \to g_1 \end{matrix} \text{ and } \begin{matrix} G \to C \\ g_2 \to c_2 \end{matrix} \qquad (4)$$

this has an overall value $r = 0{\cdot}5$.

Therefore, we see that if we are to maintain the overall r value of unity, we have to eliminate all nucleotide transformations (or pairs, etc., of transformations) which have $r < 1$ associated. Consequently, for a case, say, where two viruses, X and Y, differ in RNA composition by $C_x > C_y$ and A_x, G_x, $U_x < A_y$, G_y, U_y respectively (as is the case for TY and PV), the above diagram for possible nucleotide transformation would be restricted to $\begin{matrix} U \\ \searrow \\ A \to C \\ \nearrow \\ G \end{matrix}$ in order that r be unity.

In addition to these considerations we must determine what effect transformations in the unknown, X, factors have on the ratio r. If such a transformation occurred, it could cause the following compositional change: $\begin{matrix} A(X) \to A(X') \\ a_1 \to a_2 \end{matrix}$, with an associated r value of 0. However, when X factor transformations can be coupled (formally) to nucleotide transformations as in the following example, the resulting r value for the two taken together is unity.

$$\begin{matrix} A(X) \to A(X') \\ a_1 \to a_2 \end{matrix} \text{ and } \begin{matrix} A \to C \\ a_2 \to c_2 \end{matrix} \text{ or } \begin{matrix} G \to A \\ g_1 \to a_1 \end{matrix}$$

The entire argument above, while it does not militate against the hypothesis of Yčas, does point out that there is no *a priori* reason to suspect that, given a coding ratio $n = 1$, the ratio r should be also unity. In fact, one would *a priori* suspect that r would be less than unity. All these considerations make me feel that the hypothesis of a coding ratio $n = 1$ is somewhat artificial, and that the experimental fact $r \approx 1$ is best explained on some other basis.

Table 1. Amino-acid and Nucleotide Composition of RNA Viruses

The data on composition of the viruses is that compiled by Yčas (ref. 4); amino-acid abbreviations are those of the same reference

Amino-acid	TMV	TBS	SBM	TYV	CV	PV	Nucleotide triplet*	
ala	9·2	8·5	7·7	7·4	9·0	7·8	AGU	ala
arg	6·7	5·3	6·4	1·6	7·0	4·7	AGG	arg
asp	11·6	11·1	7·3	5·1	12·9	11·9	AGU	asp
cys	0·6	0·8	0·9	2·5	0·0	0·8	CCU	cys
glu	10·4	5·7	6·8	7·1	5·8	7·7	AUU	glu
gly	3·7	8·6	9·0	4·3	2·6	6·8	AGG	gly
his	0·0	1·2	1·3	1·4	0·0	2·4	CUU	his
ilu	5·5	3·3	6·0	8·2	4·6	4·8	ACU	ilu
leu	7·9	10·9	8·5	8·5	9·4	8·5	CGU	leu
lys	1·2	3·4	3·0	6·4	2·1	4·7	CCG	lys
met	0·0	0·8	2·6	2·0	0·0	1·5	CUU	met
phe	4·8	3·6	3·4	2·7	7·8	4·4	GUU	phe
pro	4·8	3·9	4·7	11·6	6·5	7·2	CCC	pro
ser	11·0	8·6	9·0	8·3	11·7	7·0	AAG	ser
thr	10·4	11·0	12·4	13·6	7·7	9·1	ACC	thr
try	1·2	0·5	—	0·7	0·3	—	CUU	try
tyr	2·4	2·8	4·3	1·5	2·7	3·9	UUU	tyr
val	8·5	10·0	6·8	7·4	10·0	7·2	ACG	val

Nucleotide		TMV	TBS	SBM	TYV	CV	PV
Triplet		30	27	27	24	28	25
Exp.	*A*	29	28	26	23	26	29
Yčas		28	29	28	23	26	27
Triplet		21	22	24	36	21	25
Exp.	*C*	19	21	23	38	19	22
Yčas		17	20	24	36	16	23
Triplet		25	28	26	19	27	25
Exp.	*G*	26	28	26	17	26	24
Yčas		27	27	25	18	29	24
Triplet		25	22	24	21	24	24
Exp.	*U*	27	25	25	22	30	25
Yčas		28	24	24	23	29	26

* Without regard to order within a triplet.

For this reason I have re-investigated Yčas's assertion that coding ratios greater than unity are necessarily ruled out. His proof that $r \leqslant 1/n$ is contingent on the condition that many different kinds of amino-acids contribute to $\Sigma|D_a|$. Also, the exact nature of the code will affect r somewhat. However, in order to disprove the contention that n must be unity for the RNA viruses, it is merely necessary to show that some code for which $n > 1$ is compatible with the published data. That such is the case is shown in Table 1. This triplet code was devised by the inelegant process of trial and error. There is no reason for believing that it is unique, or that one which fits the data better might not be devised. Although the agreement with experiment is not so good as with the singlet code, the code does accomplish the one end for which it was designed: to show that the composition of the six viruses is not incompatible with at least one triplet code. This relieves us of the necessity of having to assume a coding ratio of $n = 1$ and the concomitant postulate of other unidentified carriers of information not residing within the virus nucleic acid.

It will be noticed that the present code is neither a commaless code (that is, it contains *UUU* and *CCC*) nor is it a code according to Gamow's formulation (that is, order within the triplet is important). The present triplet code is examined in more detail elsewhere.

I wish to thank Dr. Martynas Yčas for stimulating my interest and for discussing his hypothesis with me.

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A SEQUENTIAL GROWTH RESPONSE TO GIBBERELLIC ACID, KINETIN AND INDOLYL-3-ACETIC ACID IN THE WHEAT COLEOPTILE (*TRITICUM VULGARE* L.)

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IN earlier work[1] the two fundamental growth processes of cell division and cell expansion in relation to the growth and differentiation of the wheat coleoptile were investigated. This was done by estimating the cell number, using the haemocytometer method of Brown and Rickless[2], and cell volume by dividing the fresh weight of the coleoptile by the respective cell number, making the usual assumption that cell volume is equivalent to the fresh weight of the cell. In these experiments the wheat (var. Eclipse) was grown at 23° C. in darkness. Whole coleoptiles were excised from young seedlings and the enclosed primary leaves teased out under a dissecting microscope. The results are presented in Table 1.

Table 1

Age of coleoptiles (hr.)	Fresh weight per coleoptile (mgm.) (± 2 s.e.)	Cell No. per coleoptile × 10^{-3} (± 2 s.e.)	Average cell volume × 10^{3} ($cm.^3$) (± 2 s.e.)
18	0·515 ± 0·019	40·15 ± 4·04	1·29 ± 0·086
24	0·625 ± 0·028	39·80 ± 3·55	1·55 ± 0·156
30	0·902 ± 0·049	40·35 ± 1·48	2·24 ± 0·11
36	1·57 ± 0·088	58·05 ± 5·64	2·73 ± 0·25
42	3·14 ± 0·25	80·3 ± 4·03	3·93 ± 0·50
48	4·40 ± 0·22	104·0 ± 7·38	4·32 ± 0·32
54	6·93 ± 0·63	118·0 ± 8·66	5·93 ± 0·98
60	10·5 ± 0·18	131·0 ± 3·54	8·01 ± 0·11
66	15·4 ± 0·23	145·0 ± 16·90	10·69 ± 1·16
72	23·5 ± 0·69	149·0 ± 6·76	14·63 ± 1·01
78		148·0 ± 12·30	
84	37·1 ± 1·8		24·9 ± 1·20
96	58·2 ± 3·4		39·1 ± 2·26
108	66·6 ± 1·7		44·7 ± 1·12
120	77·3 ± 8·4		51·9 ± 5·74
144	75·9 ± 10·6		50·9 ± 7·20

From these results the rate of increase in cell volume, cell number and coleoptile fresh weight over 6-hr. periods was calculated and the histograms are depicted in Fig. 1 *a*–*c*. The histogram representing the average rate of increase in cell volume (Fig. 1*a*) is rather misleading since the method of estimation of cell volume incorporates the negative growth-rate of cells in the process of division (that is, the volume of a cell is halved approximately when it divides), and therefore tends to under-estimate the growth-rate when cell division is taking place. A much better estimate of the average rate of increase in cell volume is given by the histogram of fresh weight for the whole coleoptile, ignoring cell number altogether. Reference to this histogram (Fig. 1*c*) shows that cell expansion in the coleoptile can be divided into two phases: an initial phase in which the rate of cell expansion increases rapidly and then falls abruptly, and a second slower, almost linear, phase of cell expansion which continues for 30 hr. before declining. A very similar histogram showing these two phases of cell expansion has also been obtained for another variety of wheat (King II).

Since it has been shown that gibberellic acid and kinetin elicit greater elongation in young tissues than in the more mature[3], it was postulated that the early rapid growth-phase in the coleoptile might be regulated by endogenous gibberellin or kinin-like substances, whereas the second, slower, linear phase of cell expansion might be invoked by endogenous auxins.

As a means of testing this hypothesis, the reaction of coleoptiles of different ages to exogenous solutions of gibberellic acid, kinetin and indolyl-3-acetic acid was investigated. This experiment was carried out in two stages. First, dosage-response curves were determined for a series of coleoptile ages for each growth regulator (Fig. 2). The wheat was grown under the conditions already described here. Four replicates of five coleoptiles (with their enclosed primary leaves) were used for each treatment. Each batch of five coleoptiles was placed in a test-tube (3 in. × ½ in.) containing 0·6 ml. of the solution to be tested, and after sealing with 'Parafilm' the tubes were transferred to a klinostat for 24 hr. at 26° C. in red light. The coleoptiles were measured before and after treatment.

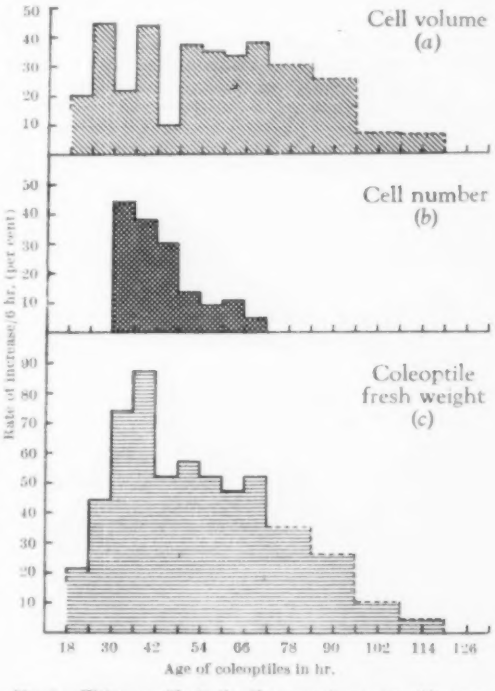

Fig. 1. Histograms illustrating the percentage rates of increase during 6-hr. periods of (*a*) the average cell volume, (*b*) cell number, and (*c*) the coleoptile fresh weight, during the growth and differentiation of the wheat coleoptile

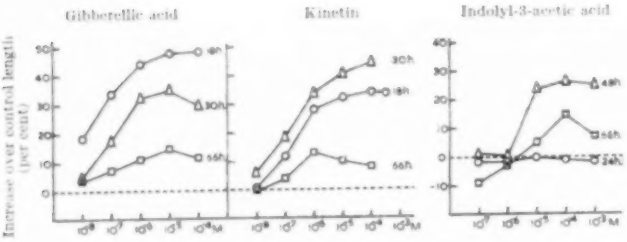

Fig. 2. Dosage-response curves for gibberellic acid, kinetin and indolyl-3-acetic acid given by coleoptiles of different ages (*h* = hours from sowing)

By referring to the dosage-response curves, it was possible to note the concentrations giving the optimal growth-response over a range of coleoptile ages for each growth regulator (Fig. 2). Thus a 10^{-5} *M* solution of gibberellic acid invoked an optimal response for coleoptiles at 18, 30 and 66 hr. after sowing and was therefore chosen to represent gibberellic acid in the final stage of the experiment. Similarly, a 10^{-4} *M* solution was selected for both kinetin and indolyl-3-acetic acid. (There was no significant difference between the growth response of 66-hr. coleoptiles to 10^{-4} *M* and 10^{-5} *M* concentrations of kinetin.)

By using only one concentration for each growth regulator, it was possible to determine the growth response of coleoptiles at 18, 30, 42, 54, 66 and 78 hr. after sowing in one large-scale experiment and thereby eliminate any inter-experimental variation in coleoptile sensitivity. These results are shown in Fig. 3 with twice *S.E.* limits. The wheat coleoptile is most sensitive to exogenously supplied gibberellic acid at or before 18 hr. after sowing, and during growth and development the response declines until at 78 hr. it is only 2 per cent above controls. Kinetin, on the other hand, gives a maximal growth stimulation at 30 hr. after sowing. Lastly, coleoptiles do not give a positive response to indolyl-3-acetic acid until 30–42 hr. after sowing and are most sensitive at about 54 hr. Thus under these experimental conditions it was established that there is a sequential growth response of the coleoptile to the three growth regulators, first to gibberellic acid, then to kinetin and finally to indolyl-3-acetic acid. This result has been obtained on three separate occasions.

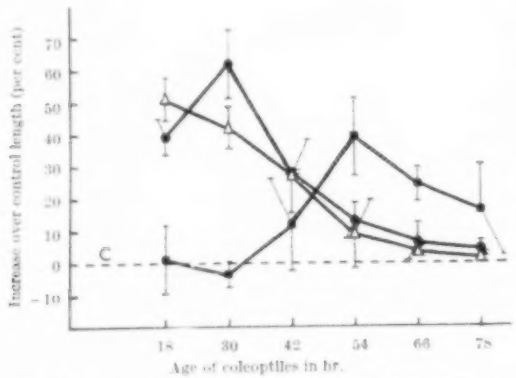

Fig. 3. Sequential growth response of the wheat coleoptile to exogenous solutions of gibberellic acid, kinetin and indolyl-3-acetic acid. The vertical lines indicate the 2 *S.E.* limits. △, Gibberellic acid, 10^{-5} *M*; ●, kinetin, 10^{-4} *M*; ■, indolyl-3-acetic acid, 10^{-4} *M*

The greatest sensitivity to gibberellic acid can be correlated with the period of cell expansion that precedes division (compare Fig. 1 *b* and *c* with Fig. 3), whereas kinetin elicits the greatest response from coleoptiles in which many of the cells are about to divide (compare Fig. 1*b* with Fig. 3). These results suggest that these two growth regulators have separate roles to take in the growth process. Nevertheless, their concerted efforts could account for the initial rapid cell expansion phase as postulated in the hypothesis above. This dual-action concept was supported by: (1) an examination of stained sections of 18-hr. coleoptiles after treatment with gibberellic acid and with kinetin for 24 hr., which showed that the growth response for both substances was due to cell expansion only; and (2) by a correlation between the rapidly falling growth-rate occurring at 42–48 hr. with a corresponding fall in sensitivity of the coleoptile to gibberellic acid, and kinetin (compare Fig. 1*c* with Fig. 3). Although indolyl-3-acetic acid did not induce cell expansion in very young coleoptiles, this does not mean that it is not required for other physiological functions and, indeed, tissue culture studies suggest that both it and kinetin are necessary for cell division[4,5].

One cannot be certain from these results that the natural growth of the coleoptile is controlled in this way by endogenous growth regulators, but evidence is accumulating in the literature for the presence of gibberellin[6,7] or kinin-like substances[5] in young tissues, and the occurrence of indolyl-3-acetic acid in oat coleoptiles (20–30 mm. long) has been claimed by several workers[8,9].

Perhaps the most plausible explanation of the sequential growth-response is that there is an optimal concentration ratio of these three types of growth regulators (and possibly others) for each stage of cell growth. One might postulate that, in a predetermined order, one concentration ratio induces the early type of cell expansion, another invokes cell division and another the final cell expansion phase. Such a coding system might operate by its action on enzyme activation or synthesis at each stage of growth[10,11]. Thus it is conceivable that cellular growth and differentiation proceed as the result of growth regulators, individually[11], or in certain concentration ratios[4,10] leading to the activation of a particular enzyme spectrum. These enzymes, by their action on their specific substrates, could in turn bring about a gradual change in the concentration pattern of the growth regulators in the cell and thereby initiate the activation of a different enzyme spectrum and so on, until differentiation is complete.

I thank Prof. R. L. Wain for his interest and encouragement in this work. The results will be reported in detail elsewhere.

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EFFECTS OF QUALITY OF LIGHT ON DEVELOPMENT OF ROOTS ON DWARF BEAN HYPOCOTYLS IN PRESENCE AND ABSENCE OF BORON

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SINCE Warington[1] discovered that boron is an element essential for growth of *Vicia faba* and demonstrated[2] that meristems cannot develop normally without it, many theories about its role have been advanced but none is entirely satisfactory. The latest theories are by Gauch and Dugger[3], who consider that boron plays a part in the transport of carbohydrate, and by Winfield[4] and Whittington[5], who postulate that it is concerned in the formation of pectic substances in the cell wall. The results described here suggest that boron metabolism is influenced by the quality of light received by the plant. Hemberg[6] found that cut plants of *Phaseolus vulgaris* with two developed leaves formed roots on their hypocotyls only when the solution bathing them contained boron. This was afterwards confirmed by Gorter[7], and Weiser[8] obtained similar results with *Clematis* cuttings. My work followed a chance observation that the extent to which roots developed on hypocotyls of cut bean plants without boron depended on whether the light supplied was from fluorescent tubes only or these tubes plus incandescent lamps.

Plants of dwarf bean (*Phaseolus vulgaris*; var. Canadian Wonder) were grown from surface-sterilized, weight-graded seed sown in John Innes compost; the plants were in cabinets at a constant ambient temperature of 20° C. and light was provided either by fluorescent tubes alone (3,500° K., white, reflector) or these were supplemented with incandescent tubes ('architectural' strip lights), when the ratio of watts consumed by the fluorescent to incandescent light was 8 : 3. Humidity was not controlled, and the plants were given a daily photoperiod of 8 or 16 hr. The light intensity at the leaf surface was 1,400 ft.-candles.

When the first pair of leaves was fully expanded and the next leaf just beginning to unfold, the hypocotyls were severed 4 cm. below the cotyledonary node, sterilized by agitation for a few seconds in hydrogen peroxide ('10 vol.'), washed in distilled water and then placed in 100 ml. conical flasks covered with black paper. The flasks contained 100 ml. of half-strength Hoagland solution + 1 mgm./l. iron as tartrate, made up in glass-distilled water further purified by passage through a mixed anion and cation exchange resin and which was stored in polythene containers. The solution in half the flasks also included 10 μgm. of boron as boric acid, because preliminary experiments showed 0·1 mgm./l. to be optimal for stimulating root growth. The flasks were of boro-silicate glass and may have supplied some boron to the plants, but, if so, they had little effect compared to added boron. The cut plants with no additional boron are referred to as the low-boron and the others as high-boron plants. While the plants were growing in the compost, before the hypocotyls were cut, they showed no signs of boron deficiency, but when the hypocotyls were severed and placed in solutions without added boron the plants quickly showed symptoms of boron deficiency.

After severing the hypocotyls, half the plants previously grown in fluorescent light were given incandescent light in addition, while the other half was maintained in fluorescent light alone. Similarly, half the plants previously given both fluorescent and incandescent light were maintained in this condition and the other half transferred to fluorescent light alone. Thus, there were four light treatments, and in each the same photoperiod was maintained both before and after severing the hypocotyl. The cut hypocotyls were placed in the different culture solutions topped up daily with the purified distilled water. After 14 days, the roots emerging from the hypocotyls were counted as well as the number of 'root initials'—the number of protrusions at the surface of the hypocotyl which failed to develop further. The total fresh weight of roots of each plant was also determined as well as the dry weight of the 4-cm. length of hypocotyl. The number of roots formed is taken to indicate the number of meristems that developed, whereas fresh weight measures the growth of the meristems. The length of hypocotyl occupied by roots was found to be constant in all treatments. A total of 136 plants was used in the 16-hr. photoperiod and 160 in the 8-hr. photoperiod.

All plants received a treatment with fluorescent light (−). Treatment in which plants received incandescent light before excision is called X, and after Y; thus, a combination of $X + Y$ indicates that the plants received incandescent light throughout the experiment. There was no effect of quality of light in the 8-hr. photoperiod and the following remarks refer mainly to results from a 16-hr. photoperiod. Table 1 shows that incandescent light given before or after excision of the hypocotyl decreased root number and total root fresh weight of low-boron plants. By contrast, the light treatments did not affect high-boron plants. As many roots were formed on high-boron plants in an 8-hr. photoperiod as in a 16-hr. period, but the shorter day-length decreased the number of roots formed by low-boron plants. In addition to affecting root formation, boron alters the response to the type of light. Although estimates of root initials are subjective and those in Table 1 are only approximate, they show that root initials were few with treatments that formed roots freely, and many with others. Thus, root initials usually varied inversely with the number of roots, but roots and root initials together totalled many more with high-boron than low-boron plants. Root fresh weight varied with root number, with the additional effect

Table 1. Mean Number of Roots and Root Initials, Root Fresh Weight and Hypocotyl Dry Weight of Bean Plants Subject to Incandescent and Fluorescent Light in Low- and High-Boron Solutions

	8 hr. − boron			8 hr. + boron			16 hr. − boron			16 hr. + boron		
	(−)	*X*	Mean	(−)	*X*	Mean	(−)	*X*	Mean	(−)	*X*	Mean
No. of roots	[a]4·1	8·2	[b]6·1	[a]50·4	41·3	[b]45·9	[a]30·9	11·2	[b]21·0	[a]49·0	50·5	[b]49·7
Y	6·5	1·7	4·1	44·1	43·3	43·7	17·3	8·5	12·9	48·4	44·5	46·5
Mean	[b]5·3	4·9	5·1	[b]47·2	42·3	44·8	[b]24·1	9·8	17·0	[b]48·7	47·5	48·1
L.S.D.		*a* = 6·64	*b* = 4·70		*a* = 9·08	*b* = 6·42		*a* = 7·20	*b* = 5·09		*a* = 9·84	*b* = 6·96
No. of root initials	[a]18·5	14·9	[b]16·7	[a]2·6	6·6	[b]4·6	[a]13·8	16·5	[b]15·2	[a]1·0	2·3	[b]1·6
Y	17·7	16·0	16·9	3·8	3·4	3·6	12·2	17·1	14·6	3·3	2·7	3·0
Mean	[b]18·1	15·4	16·8	[b]3·2	5·0	4·1	[b]13·0	16·8	14·9	[b]2·2	2·5	2·3
L.S.D.		*a* = 3·68	*b* = 2·61		*a* = 2·24	*b* = 1·58		*a* = 4·09	*b* = 2·89		*a* = 2·12	*b* = 1·51
Fresh weight roots (mgm.)	[a]25	43	[b]34	[a]230	196	[b]217	[a]335	99	[b]217	[a]350	374	[b]362
Y	41	11	26	232	202	217	204	89	147	313	295	304
Mean	[b]33	27	30	[b]235	199	217	[b]270	94	182	[b]332	334	333
L.S.D.		*a* = 63·3	*b* = 44·8		*a* = 68·0	*b* = 48·1		*a* = 68·6	*b* = 48·5		*a* = 73·9	*b* = 52·8
Dry weight hypocotyl (mgm.)	[a]66·4	68·7	[b]67·6	[a]68·9	65·4	[b]67·1	[a]95·1	84·5	[b]89·8	[a]101·9	93·9	[b]97·9
Y	74·3	65·1	69·7	71·1	64·3	67·7	98·7	87·6	93·2	89·1	92·3	90·7
Mean	[b]70·4	66·9	68·6	[b]70·0	64·8	67·4	[b]96·9	86·1	91·5	[b]95·5	93·1	94·3
L.S.D.		*a* = 7·50	*b* = 5·30		*a* = 8·18	*b* = 5·79		*a* = 8·15	*b* = 5·76		*a* = 8·85	*b* = 6·26
Fresh weight per root (mgm.)	6·1	5·2	5·6	4·7	4·7	4·7	10·8	8·8	9·8	7·1	7·4	7·3
Y	6·3	6·5	6·4	5·3	4·7	5·0	11·8	10·5	11·1	6·5	6·6	6·5
Mean	6·2	5·8	6·0	5·0	4·7	4·8	11·3	9·6	10·5	6·8	7·0	6·9

(−), fluorescent light. *X*, incandescent light before excision. *Y*, incandescent light after excision.

that incandescent light after excision decreased fresh weight of high-boron plants also. Incandescent light, however, affected low-boron plants more, for without it plants had similar root fresh weights whether or not they were given boron (350 and 335 mgm.). In other words, boron deficiency restricts root growth only with incandescent light. Although boron increased the number of roots, the low-boron plants had greater fresh weight per root than high-boron plants in both photoperiods (Table 1), perhaps because the fewer meristems of low-boron plants suffered less competition for products of photosynthesis. Similarly, the primary leaves of whole bean plants grown in water culture without boron were larger than those grown with boron (boron-deficient plants had a mean midrib length of 70 mm. and those with boron 65 mm., based on a sample of 360 plants), possibly because nutrients which would normally go to the growing point are diverted to the leaves when the growing point aborts in boron-deficient conditions[8].

The growth of the hypocotyl was decreased in low-boron plants by incandescent light given before excision but not after. By contrast, incandescent light decreased hypocotyl dry weight in high-boron plants after excision. Thus, boron had little effect on root formation in plants illuminated only with fluorescent light; but with incandescent light, root formation depended on added boron.

The leaves were fully illuminated but little radiation reached the submerged hypocotyl, because covers on the flasks excluded lateral illumination and direct illumination was confined to the narrow opening of the flask partly obscured by the primary leaves. The action of light on root formation can therefore be assumed to be indirect. Incandescent light inhibited root formation only in the 16-hr. photoperiod, perhaps only because too few roots formed on low-boron plants in an 8-hr. photoperiod to show differences. Any inhibition presumably arises in the leaf and persists after the hypocotyl is severed. How inhibition by incandescent light is linked with boron deficiency is uncertain, but there are several possibilities. For example, boron may protect a root-promoting substance from destruction by incandescent light or perhaps incandescent light affects mobility of boron in the plant.

The site where the light stimulus interacts with boron depends on the mobility of boron in the cut plants. Published evidence that boron is rather immobile is confirmed in my experiments. The soil contained enough boron for growth of the plants, but as soon as the hypocotyl was severed, more was necessary for meristems to develop in both root and shoot, indicating that boron already in the plant could not serve for this. Scholz[10], in experiments using single tobacco leaves with a divided root system, found that boron was not transferred from roots supplied with boron to those without it, but accumulated in the leaf. He concluded that boron moves only in the direction from root to shoot, and Albert[11] came to a similar conclusion. When I treated leaves of boron-deficient plants with boron solution, boron was evidently translocated to the hypocotyl, because meristem development was stimulated, and in the experiments described above boron was transferred from the solution bathing the hypocotyl to the shoot, because apical meristem development continued in these plants. Evidently under these conditions boron is translocated either upwards or downwards, but perhaps this applies only to inorganic boron, and conditions in intact plants may be different. The evidence does not show where boron and the light stimulus interact.

In some respects boron resembles indoleacetic acid in stimulating root formation on hypocotyls; but indoleacetic acid and boron differ in that the former is necessary to stimulate meristem activity, whereas, as Hemberg (*loc. cit.*) points out, the latter does not affect the formation but only the growth of roots; hypocotyls grown in media deficient in boron develop wart-like elevations (called 'root initials' here), which do not develop into roots. It seems unlikely, therefore, that the present phenomenon is concerned with indoleacetic acid metabolism. My experiment suggests a connexion between radiation in the red or far-red part of the spectrum that inhibits root-growth when boron is a limiting factor, but this has yet to be investigated fully. That light and boron metabolism may be connected is suggested by other work. Symptoms of boron deficiency develop sooner and more severely in long than short days (Gauch and Dugger[9]) and Stegemann[12] concluded that the action of radiation is regulated by boron. Albert[11]

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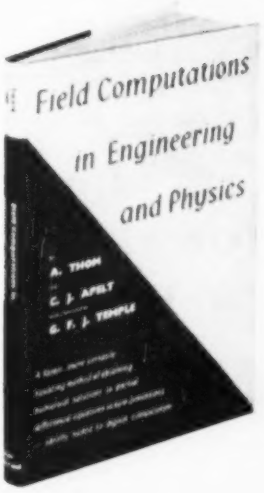

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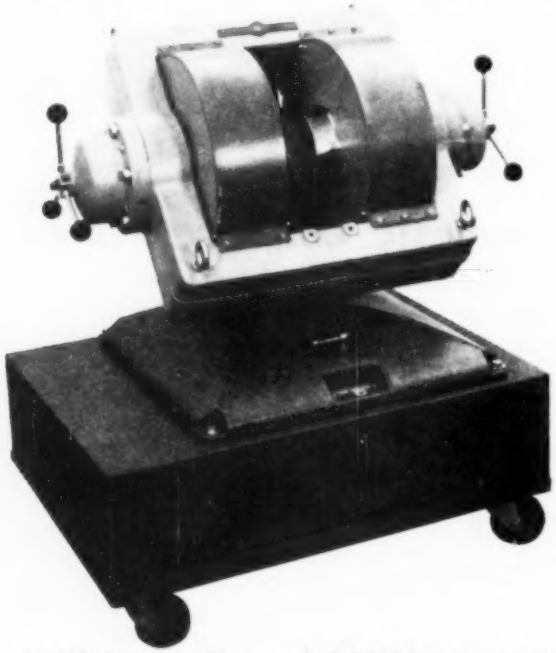

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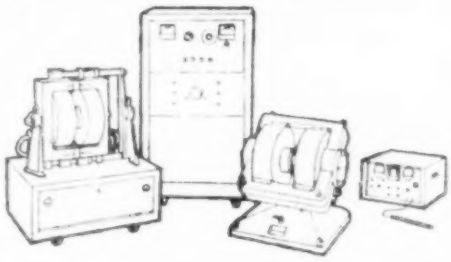

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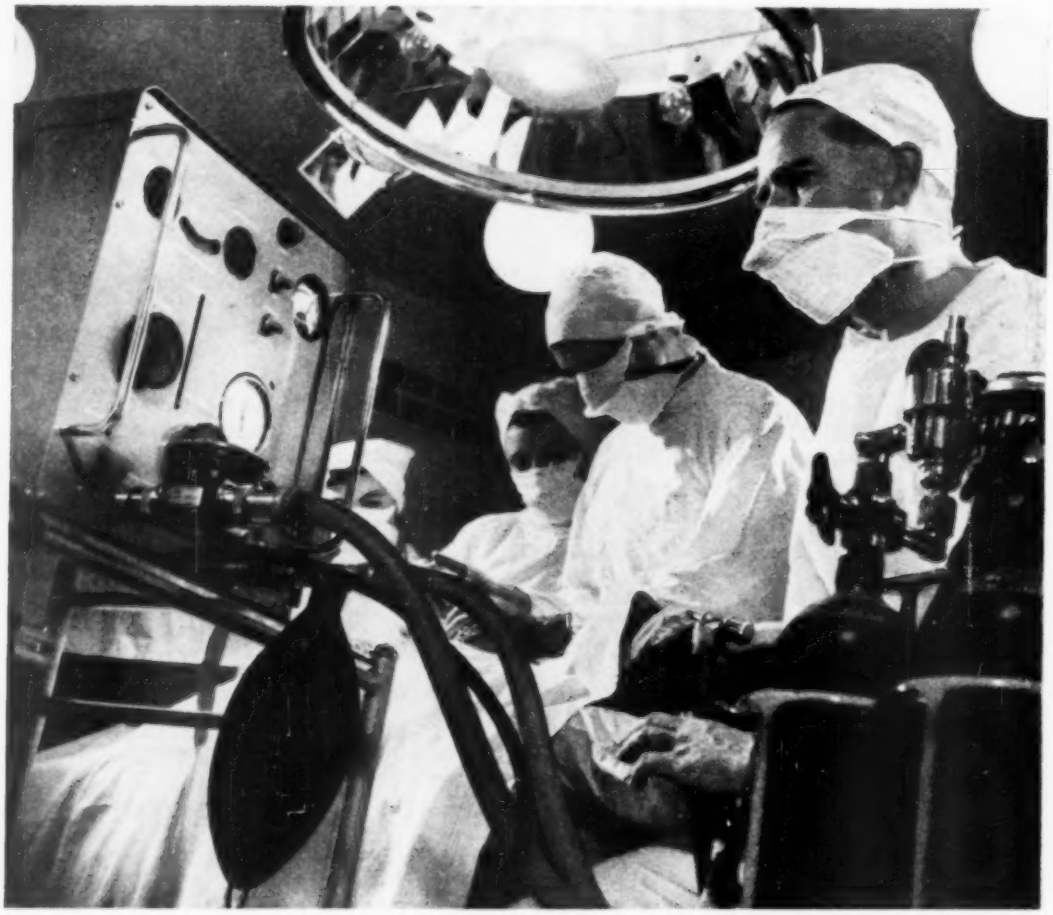

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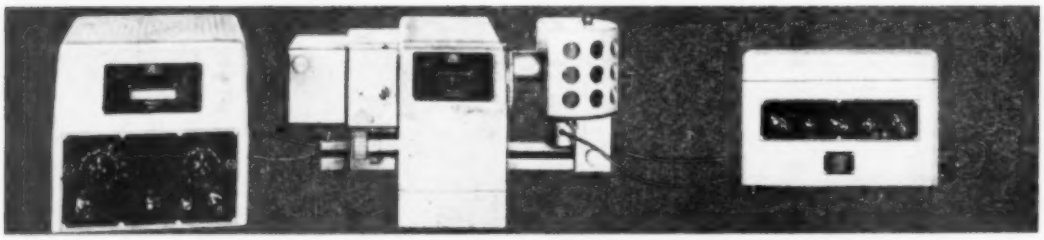

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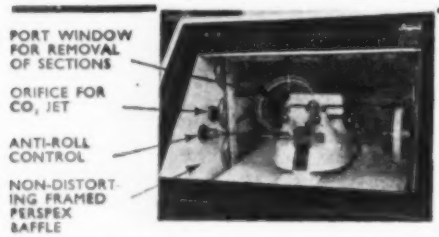

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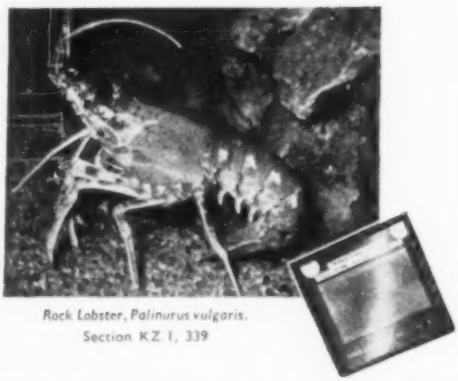

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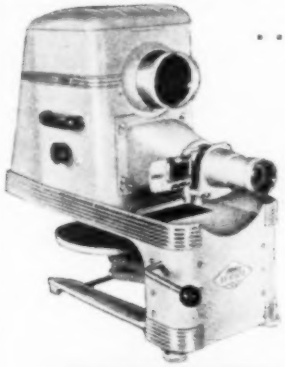

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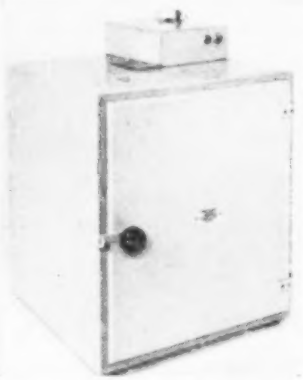

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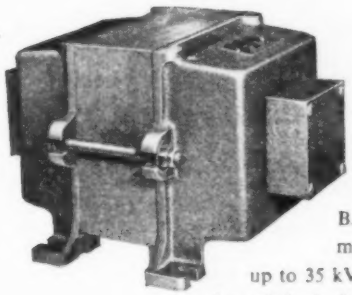

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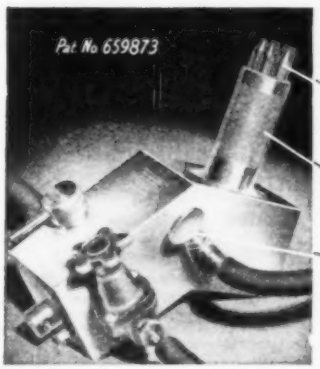

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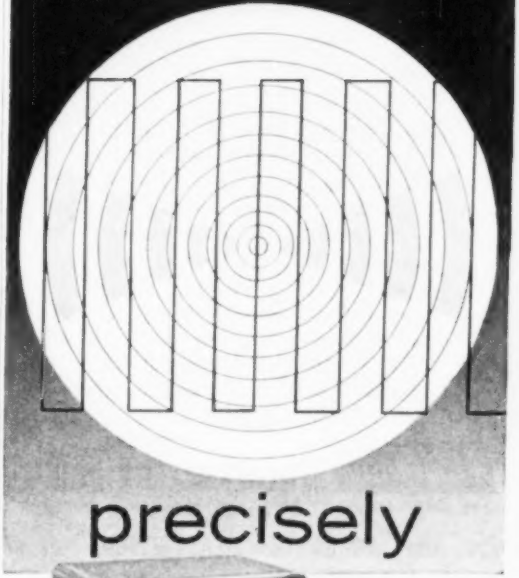

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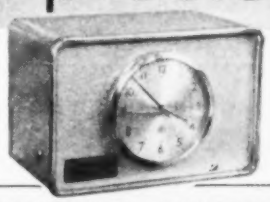

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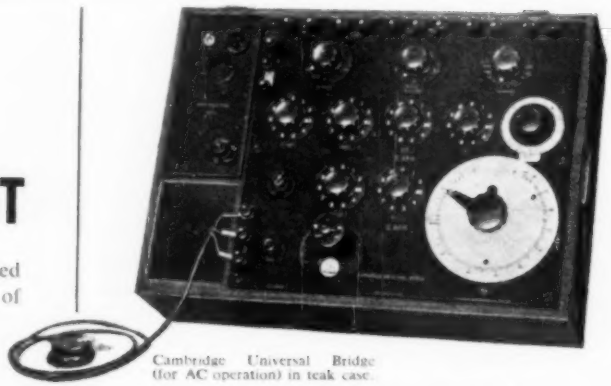

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suggested that some factor, other than carbohydrate, present in the top of the plant, is affected by light and may influence the response of tomato plants to boron deficiency. Skok[12] found that sunflower leaves were more radiosensitive with than without boron.

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AN ESTIMATE OF THE AROMATICITY OF THE ORGANIC MATTER OF A PODZOL SOIL

By Dr. J. R. WRIGHT and Dr. M. SCHNITZER

Soil Research Institute, Department of Agriculture, Ottawa, Canada

IN our work on the chemical structure of the organic matter of the A_0 and B_h horizons of a podzol we were interested in a practical method for estimating the aromaticity of these materials. Such a method has recently been described by Mazumdar *et al.*[1] and Chakrabartty *et al.*[2] for determining the aromaticity of lignite, bituminous and higher-rank coals. Since soil organic matter resembles lignites and brown coals in many respects, we thought application of this procedure to such material might yield valuable information with regard to its aromaticity. As a check on our technique, we included a sample of lignite in this investigation because values for the aromaticity of this material are available in the literature.

According to Mazumdar *et al.*[1], heating of coal in air at 170° C. for approximately 500 hr. causes the complete oxidation of the 'disordered' (aliphatic and alicyclic) carbon while leaving the aromatic network intact. The oxidation of the 'disordered' carbon results in the formation of oxygen-containing functional groups, mainly carboxyls. Therefore, the only aliphatic carbon and hydrogen in the final oxidized product is that in carboxyl groups. Thus the total carbon and hydrogen in the final oxidized product, corrected for the carboxylic carbon and hydrogen, gives the total aromatic carbon and hydrogen present in the original material. In addition, in the case of hydrogen, it is necessary to correct for hydrogen replaced by quinone groups[2].

The soil samples and methods of extraction of organic matter were the same as those described previously[3] except that all extractions were made under nitrogen and the extracts were dried under reduced pressure at room temperature. The lignite sample originated from the Souris, Manitoba, area. Carboxyl groups were determined by reaction with calcium acetate[4], phenolic hydroxyls by reaction with barium hydroxide under nitrogen and correcting for carboxyls[5]. Carbonyls were determined by the method of Fritz *et al.*[6] and ultimate analyses by dry combustion.

1-gm. samples, spread in thin layers in aluminium dishes, were heated in an oven at 170° C. for various lengths of time up to and including 600 hr. A current of air was passed through the oven at a constant rate. Samples were withdrawn every 100 hr., weighed and analysed for functional groups and ultimate composition. Under these heating conditions, Mazumdar and Lahiri[7] reported that lignite and higher-rank coals reached constant weight after 300–400 hr. With our samples the A_0 material reached constant weight at approximately 500 hr. while the lignite and B_h preparation still continued to lose weight although the rate of loss was low (1·8 and 1·6 per cent in the 500–600 hr. period). In view of these findings we adopted a heating period of 600 hr. for all samples.

All results shown in Tables 1–4 under "after oxidation" refer to 600 hr. of heating.

Heating caused an increase in the carbon contents of the A_0 and B_h materials and a decrease in that of lignite (Table 1). All materials reached a constant carbon content between 200 and 300 hr. Most of the hydrogen was lost during the first 100 hr. This is in agreement with the findings of Chakrabartty *et al.*[8] that dehydrogenation appears to be the main reaction in the initial stages of coal oxidation. After 600 hr. of heating, 100, 93 and 87 per cent of the original nitrogen still remained in the oxidized residues of the lignite, B_h and A_0 materials respectively.

The carboxyl contents of the original lignite, A_0 and B_h materials were 2·0, 6·7 and 40·9 per cent respectively. In the case of lignite the carboxyl content increased to a constant value after about 400 hr. of oxidation. On the other hand, the carboxyl contents of the A_0 and B_h materials decreased during the initial stages of the oxidation. This was followed by a slight rise with constant values being obtained after 400 hr.

The values for carbon aromaticity (Table 2) represent aromatic carbon as a fraction of total carbon. The values in brackets represent aromatic carbon as a fraction of total carbon less carboxyl carbon. These values are shown in order to give an estimate of the aromaticity of the carbon skeleton. As shown in Table 2, the two values for lignite are identical because this material and higher-rank coals contain few or no carboxyl groups prior to oxidation in contrast to soil organic matter preparations. The value of 0·56 for the aromaticity of lignite agrees well with that reported by Chakrabartty *et al.*[2]. The hydrogen aromaticity, similar to the carbon aromaticity, was calculated on the basis of both total hydrogen and total hydrogen minus carboxyl hydrogen (Table 3). Hydrogen aromaticity of the lignite analysed by Chakrabartty *et al.*[2] was 0·29.

Infra-red spectra of the A_0 and B_h materials taken at various stages of the oxidation showed a gradual decrease and finally complete disappearance of the 2,920 and 2,850 cm.$^{-1}$ bands (aliphatic C—H). After 50 hr. of heating the infra-red spectra of the B_h material showed new bands at 1,840 and 1,775 cm.$^{-1}$ which, together with the band already present at

Table 1. Analytical Characteristics Before and After Oxidation
(all data on dry ash-free basis)

Sample	Loss in weight (per cent)	C (per cent)	H (per cent)	Atomic ratio (H/C)	N (per cent)	Functional group analysis: O_{COOH} (per cent)	Functional group analysis: O_{OH} (phenolic) (per cent)	Functional group analysis: O_{CO} (per cent)	Functional Group O: Total O
A_0 Before oxidation	50·2	56·72	5·21	1·10	2·37	4·7	6·6	1·5	0·38
After oxidation		58·79	3·81	0·78	4·17	4·0	7·3	3·0	0·45
B_0 Before oxidation	40·8	50·92	3·34	0·79	0·74	29·1	5·3	5·0	0·90
After oxidation		56·21	2·08	0·44	1·16	23·7	10·0	8·1	1·03
Lignite Before oxidation	34·2	65·13	4·30	0·79	0·92	1·3	6·6	5·0	0·46
After oxidation		61·58	2·60	0·51	1·44	11·2	10·1	1·9	0·73

Table 2. Carbon Aromaticity
(based on the oxidation of 100 gm. of dry ash-free material)

Sample	Input* C (gm.)	Output* C (gm.)	C_{COOH} in oxidized residue* (gm.)	Aromatic C (gm.)	Non-aromatic C (gm.)	Aromaticity f_a
A_0 Before oxidation	56·72 (54·92)†	29·28	1·50	27·78	28·94	0·49 (0·51)†
After oxidation						
B_0 Before oxidation	50·92 (40·00)†	33·28	8·87	24·41	26·51	0·48 (0·61)†
After oxidation						
Lignite Before oxidation	65·13 (64·60)†	40·52	4·20	36·32	28·81	0·56 (0·56)†
After oxidation						

* See Table 1.
† Corrected for C_{COOH} in original material.

Table 3. Hydrogen Aromaticity
(based on the oxidation of 100 gm. of dry ash-free material)

Sample	Input* H (gm.)	Output* H (gm.)	Correction for: H_{COOH} (gm.)*	Correction for: Aromatic H (gm.)* (H replaced by quinone)	Aromatic H (gm.)	Non-aromatic H (gm.)	H arom. / H	H non-arom. / H	Atomic ratio H arom. / C	Atomic ratio H non-arom. / C
A_0	5·21 (5·06)†	1·89	− 0·13	+ 0·10	1·86	3·35 (3·20)†	0·36 (0·37)†	0·64 (0·63)†	0·39 (0·41)†	0·71 (0·70)†
B_0	3·34 (2·42)†	1·23	− 0·74	+ 0·20	0·69	2·65 (1·73)†	0·21 (0·29)†	0·79 (0·71)†	0·16 (0·21)†	0·63 (0·52)†
Lignite	4·30 (4·26)†	1·72	− 0·35	0	1·37	2·93 (2·89)†	0·32 (0·32)†	0·68 (0·68)†	0·26 (0·26)†	0·54 (0·54)†

* See Table 1.
† Corrected for H_{COOH} in original material.

Table 4. Distribution of Carbon and Hydrogen in the Original Materials

Sample	Carbon: Aromatic (%)	Carbon: In COOH groups (%)	Carbon: Aliphatic and/or alicyclic (%)	Hydrogen: Aromatic (%)	Hydrogen: In COOH groups (%)	Hydrogen: Aliphatic and/or alicyclic (%)
A_0	49	3	48	36	3	61
B_0	48	22	30	21	28	51
Lignite	56	1	43	32	1	67

1,200 cm.$^{-1}$, indicated the probable formation of cyclic anhydrides[9]. Also, new bands appeared at 920 cm.$^{-1}$ (OH deformation vibrations of COOH) and at 740 cm.$^{-1}$ (polycyclic aromatic structures). All these bands increased in intensity with heating. From the infra-red spectra we estimated that not more than 10 per cent of the carboxyl groups of the B_0 material had formed anhydrides. On this assumption the correction for H_{COOH} (Table 3) should be 10 per cent lower resulting in a correspondingly higher hydrogen aromaticity.

A carbon and hydrogen balance is shown in Table 4. Exclusive of the carboxylic carbon and hydrogen, the A_0 material contained more aliphatic and/or alicyclic carbon and hydrogen than the B_0 preparation. This would indicate that the carbon skeleton of the B_0 is more aromatic than that of the A_0 material. Similar conclusions were reached from oxidative degradation studies of these two materials[10].

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LETTERS TO THE EDITORS

RADIOASTRONOMY

Secular Variation of the Flux Density of the Radio Source Cassiopeia A

Högbom and Shakeshaft[1] have recently presented evidence for a secular variation of the intensity of radio emission from the source Cassiopeia A. Their observations, made at a frequency of 81·5 Mc./s. over a period of 12 years, suggest that the flux density of Cassiopeia A relative to that of Cygnus A is decreasing at a rate of about 1 per cent per annum. This type of measurement may be sensitive to unknown systematic instrumental effects, and the importance of the result makes independent confirmation desirable.

Observations of the ratio of flux densities of Cassiopeia A and Cygnus A were begun at the National Radio Astronomy Observatory in 1959, in order to search for a possible change in intensity of Cassiopeia A. While these observations cover a period of only one year, they do, in conjunction with earlier observations at about the same frequency obtained at other observatories, provide some confirmation of the result of Högbom and Shakeshaft.

The available 1,400-Mc./s. observations of the ratio of Cassiopeia A to Cygnus A are given in Table 1. The Leyden[2], Bonn[3] and National Radio Astronomy Observatory[4] observations were made with antennae of about the same diameter, 82–85 ft., and were corrected for atmospheric extinction and receiver non-linearity. The Naval Research Laboratory observations[5] were made with a 50-ft. diameter antenna. The Leyden, Bonn and National Radio Astronomy Observatory observations all have small internal uncertainties. Systematic effects should also be small, as in each case the observational procedures were specifically selected to minimize them so far as possible. Although the Naval Research Laboratory measurements are of lower accuracy than the others they are of particular value because they are the earliest measurements of these sources at this frequency. Details of the equipments, observing techniques and reduction procedures used in the various measurements are given in the references cited.

Fig. 1 shows the 1,400-Mc./s. flux density ratios as a function of time. The solid line in Fig. 1 represents the change in Cassiopeia A/Cygnus A at 81·5 Mc./s., found by Högbom and Shakeshaft. The 1,400 Mc./s. observations suggest a secular change in reasonable agreement with that found at 81·5 Mc./s. The vertical displacement of the 1,400 Mc./s. and 81·5 Mc./s. ratios is due to the difference in spectra of the two sources.

Table 1

Date	Cas. A/Cyg. A	Frequency (Mc./s.)	Source
1954	1·8 ± 0·1	1,394	NRL
1956	1·63 ± 0·01	1,395	Leyden
1958	1·63	1,419	Bonn
1959	1·608 ± 0·003	1,400	NRAO
1960	1·592 ± 0·003	1,400	NRAO

NRAO, National Radio Astronomy Observatory.

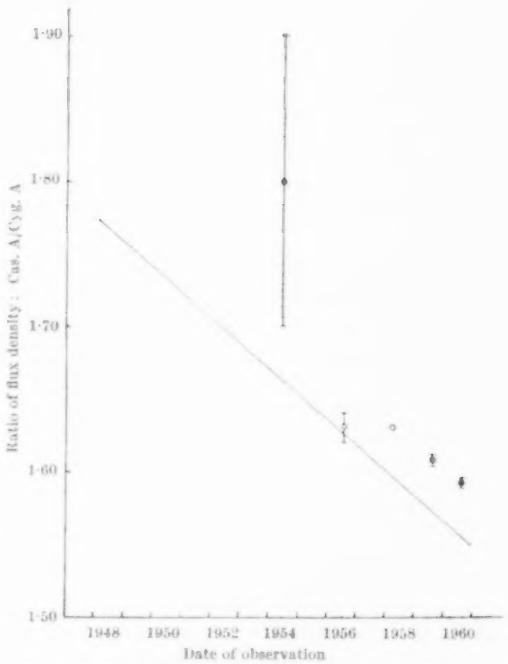

Fig. 1. Variation of the ratio of intensities of Cassiopeia A and Cygnus A as a function of time. Points with circles give measurements at a frequency of 1,400 Mc./s. Vertical lines show the published uncertainties in the measurements. No estimate of error was given for the 1958 measurement. The solid line is the variation of Cas.A/Cyg. A with time at 81·5 Mc./s., as found by Högbom and Shakeshaft (ref. 1)

The 1960 result, given in Table 1 and Fig. 1, is the mean of sixteen sets of observations made at one-week intervals in the period June 17–September 30, 1960. These observations were made with the same receiver and antenna, under as nearly identical conditions as possible. They have high relative accuracy and should be largely free of any systematic

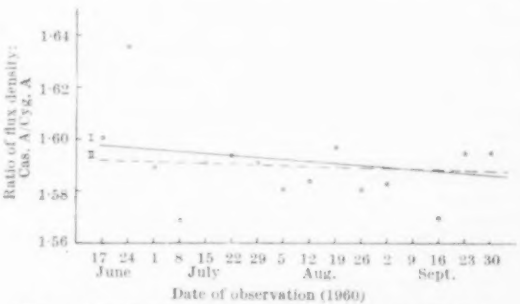

Fig. 2. Weekly measurements of Cas. A/Cyg. A at 1,400 Mc./s. The solid line (I) is the least squares straight line which best fits all the measurements. The dashed line (II) is the straight line which best fits the data if the four least accurate measurements are omitted

instrumental effects over the time-interval involved. The weekly measurements are shown in Fig. 2. Even over this short interval of time there is evidence of a systematic change in the ratio of Cassiopeia A to Cygnus A flux density. A least-squares solution for the best straight line representing all sixteen measurements gives a rate of decrease of 2·3 per cent per annum. This solution is shown by the solid line (I) in Fig. 2. A second solution was made omitting the four days on which the measurements deviated from the mean value by more than five standard errors. On two of these days (June 24 and July 8) the observer had noted on the records as they were obtained the probability of interference or marginal receiver performance. This solution, indicated by the dashed line (II) in Fig. 2, gives a rate of decrease of 0·9 per cent per annum. Both values are in good agreement with the results of Högbom and Shakeshaft.

The 1,400-Mc./s. measurements are not sufficiently accurate to determine the rate of decrease of intensity of Cassiopeia A with any reliability, so the question as to whether the rate of change is independent of frequency remains open.

We wish to thank Messrs. Högbom and Shakeshaft for a copy of their paper prior to its publication.

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Green Bank, West Virginia.

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ASTROPHYSICS

Solar Wind and Terrestrial Oxygen

Stefansson[1] pointed out that nothing gained such universal acceptance as an error. This should make us all wary of unanimity, and it has led me to question persistently the general assumption that Earth's original atmosphere contained little or no oxygen and that the origins of life are to be sought exclusively among anaerobic reactions. The atmosphere now contains 230 gm. of oxygen per sq. cm. and perhaps twice that amount must have passed through the atmosphere at an early stage of Earth's development to account for ferric iron, sulphates, etc., in sediments. These quantities are so small that slightly different assumptions lead to radically different conclusions about the amount of oxygen at various times during the past 3×10^9 years. It has, nevertheless, been difficult to account satisfactorily for the oxygen and there is opposition to all the mechanisms proposed for its formation.

Those interested in the origins of life are therefore eager for comment on the suggestion[2] that Earth is gaining 1·5 tons of hydrogen a second from the solar wind, for this rate of accretion would provide all the hydrogen in the ocean in 3×10^9 years. If this is so, the oxygen in the ocean comes into the category of 'fossil oxygen' along with ferric iron. There are 230 kgm. of it per sq. cm., that is, 500 times the amount that has been causing trouble hitherto. If we exist, and have always existed, in this hydrogen hurricane, the problem of the origin of oxygen is more intractable than we thought.

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Harpenden, Herts.

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RADIOPHYSICS

Variation in Height of Anisotropy and Random Drift Velocity of the Irregularities in the Ionosphere

Horizontal ionospheric drift records taken by the spaced receiver method of Mitra[1] are used here to analyse the variation with height of anisotropy and random drift speed $(V_c)_r$ along the direction of steady drift of the irregularities.

Horizontal drift records were taken in rapid succession on several frequencies corresponding to different levels of reflexion on six days around the morning hours of 0900 I.S.T. The drift records were analysed by Phillips and Spencer's[2] correlation method to determine the steady and random drift velocities as well as the axial ratio r and orientation of the anisotropy ellipse. It is generally assumed that these values refer to the irregularities in the ionosphere. The true height of reflexion corresponding to each drift record was calculated, using Schmerling's[3] method, from an $h'(f)$ record taken at the same time.

Values of ν, the orientation of the major axis of the correlation ellipse in degrees east of north, showed no preferred direction, a feature which has also been reported earlier by Phillips and Spencer. However, on each occasion, the variation of ν with height in the ionosphere was found to be very systematic. A clockwise rotation of the major axis with increasing height is clearly evident on five of the six occasions. The gradient $\partial\nu/\partial h$ was found to vary between 54′ to 1° 42′ km.$^{-1}$ with an average of 1° 28′ km.$^{-1}$.

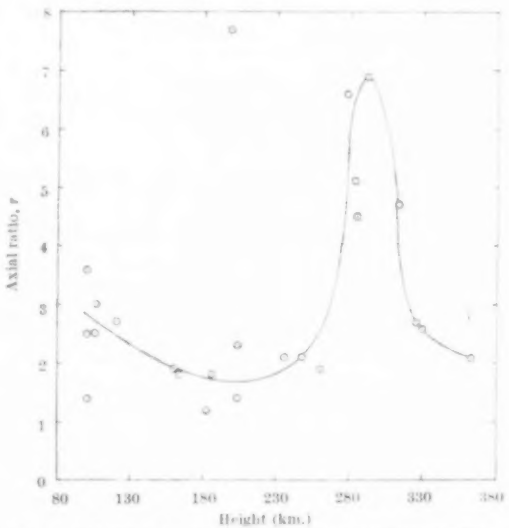

Fig. 1. Variation in height of axial ratio of the anisotropy ellipse

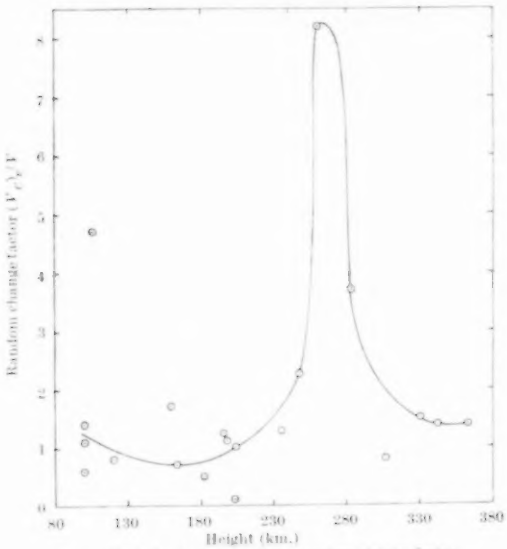

Fig. 2. Variation in height of the random change factor

The axial ratio r also showed a more or less systematic variation with height. In Fig. 1 is presented a plot of the axial ratio variation with height for all the six days. A smooth curve is drawn which passes through most of the observations. It can be seen that r decreases with height at first, slowly from about 100 km. to 190 km., then rises rapidly, reaching a maximum value of about seven at a height of about 290 km. Above this height, the value of r is found to decrease rapidly.

In Fig. 2 is presented a plot of the 'random change factor' $(V_C)_R/V$ versus height, where V is the steady drift velocity of the diffraction pattern on the ground. In this case, too, a smooth curve is drawn passing through most of the observations. This plot of $(V_C)_R/V$ is very similar to that in Fig. 1, except that the peak occurs at about 270 km. instead of at 290 km. It appears, from this work, that the ionospheric irregularities are highly elongated in regions where random motion predominates over the steady drift. It may be of interest here to point out that Yerg[4] also arrived at a similar conclusion when he stated that "large random changes are anisotropic and tend to cause the correlation pattern to be oriented along the magnetic field", although the latter trend is not clearly observed in our investigation. It is, thus, quite possible that, at this latitude, the irregularities responsible for the radio-star scintillations and spread F are located at about the level of 270–290 km. since $(V_C)_R/V$ and r are each a maximum in this region. However, it may be pointed out that the investigations were conducted by us only during daytime. Booker[5] suggested that radio-star scintillations cannot be explained in terms of turbulence if the height of irregularities causing the scintillation phenomena were taken to be located at 400 km. He concluded from certain theoretical considerations that a reasonable explanation can be offered for the scintillation phenomena if that height is about 200–300 km. The observation of large random drift velocities and also of intense spread F in the range of 200–300 km. at this station seems to lend support to this view.

A detailed paper on the investigations will be published elsewhere. We are indebted to the Council of Scientific and Industrial Research for supporting this investigation.

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Irregularities in the E_s Layer of the Ionosphere

It has been shown from oblique incidence backscatter experiments that the equatorial type of sporadic E ionization (E_s) contains irregularities which are elongated in a north–south direction, that is, along the direction of the Earth's magnetic field[1]. On the other hand, observations made at high latitudes have shown that the auroral type of E_s layer contains irregularities which are elongated in an east–west direction, that is, perpendicular to the field[2]. The results in the second case were based on observations of the diffraction pattern produced on the ground by a reflected wave. No corresponding observations relating to the E_s layer in medium latitudes have been reported.

In the present communication, some observations made at Cambridge (lat. 52° N., long. 0° E.) are described. The method was based on measurements of the diffraction pattern produced by a wave reflected at vertical incidence. The transmitted pulses were 100–200 μs. in length, and the frequencies used were in the range 4·0–4·5 Mc./s. during the day, and 2·0–2·4 Mc./s. at night. The reflected waves were received on three crossed-loop aerials, arranged to accept the 'ordinary' circularly polarized component of the down-coming wave, and placed at the corners of a right-angled triangle having two equal sides 130 m. long in the north–south and east–west directions. The amplitudes of the received pulses were recorded using a pen-recorder, or on film if the fading became too fast to be recorded faithfully by the pen-recorder. Correlation analysis was applied to typical portions of the records for eighteen occasions between March 1959 and August 1960. The auto- and cross-correlation functions of the fading curves were calculated using an electronic digital computer, and the graphical method of Phillips and Spencer[3] was used in subsequent calculations to determine the properties of the diffraction pattern.

The results of the analysis show great variability in the scale of the irregularities in the diffraction pattern on the ground. For only nine of the eighteen occasions was it possible to determine a characteristic ellipse representing an average single irregularity in the pattern; on the other occasions the irregularities were either very large (1 km. approximately) or very small (80 m. approximately) and their scale could only be estimated very roughly.

While it is not possible in general to determine the size of irregularities in the ionosphere simply from measurements of amplitude in the diffraction pattern on the ground[4], the axial ratio and orientation of the characteristic ellipse of the diffraction pattern do give

a measure of the elongation and orientation of the irregularities in the ionosphere. When the characteristic ellipse could be found, it was not usually very elongated; on only three of the nine occasions was the axial ratio greater than 2·0, and there was no evidence of any preferred direction of elongation. This is in contrast with the systematic elongation found at high and low latitudes.

On all the occasions when the fading of waves reflected from the E_s layer was observed at Cambridge, E_s was also found on ionograms obtained at Slough, 90 km. to the south-south-west. There was, however, no apparent association between the scale of the irregularities in the diffraction pattern at Cambridge and the type of E_s (*c*, *f*, *h* or *l*) as determined by its appearance on the Slough ionogram[5]. There was also no association between the scale of the pattern and the magnetic *K*-index (*K* was in the range of 0–4 for the occasions observed).

This work forms part of a programme of research on ionospheric irregularities supported by a grant from the Department of Scientific and Industrial Research. I was in receipt of a maintenance grant from the same Department. Thanks are due to the Director of the Mathematical Laboratory, University of Cambridge, for permission to use the computer *Edsac* 2.

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108–216 Mc./s. Radio Signals from Satellites below the Horizon

Smyth Research Associates have been conducting an experimental programme on low-angle refraction of radio waves penetrating the atmosphere.

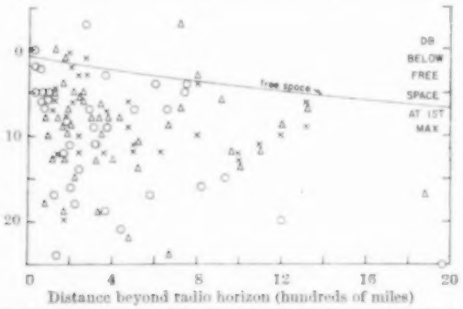

Fig. 1. Precursor signal-levels. ○, 108 Mc./s.; ×, 162 Mc./s.; △, 211 Mc./s.

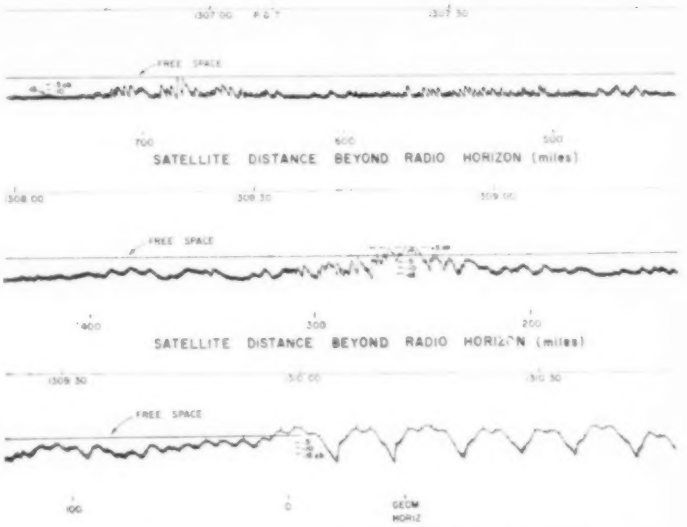

Fig. 2. Satellite precursor signals. Tiros I, 108 Mc./s. June 13, 1960

Satellite transmitters at 108, 162, and 216 Mc./s. have been used as signal sources in these studies. During the course of the measurements (June, July and August 1960) it was found that, on the majority of passes, signals were received while the satellite was well beyond the radio horizon. Out of a total of 49 cases when such 'precursor' signals were sought, only 14 failed to yield signals for at least one minute beyond the radio horizon.

In two cases, signals were first received when the satellite was 1,900–1,950 miles beyond the radio horizon point at orbit height. On these passes the satellite was roughly twice as far away as the distance to the horizon. The signal strength on these occasions was 11 db. below the free space-level on 216 Mc./s. and 18 db. below the free space-level on 108 Mc./s. As can be seen in Fig. 1, there appears to be no distinct dependence of received signal strength on frequency. Even simultaneous data on 162 and 216 Mc./s. show no consistent dependence on frequency.

The combination of low attenuation and no frequency-dependence suggests a tropospheric ducting mechanism. Correlation of local radiosonde data with signal strength and maximum path-length supports this view. The duct thickness and intensity in all cases when signals were observed exceeded the trapping requirements for frequencies greater than 100 Mc./s.

Fig. 2 shows the data record for one of these cases, together with a scale of the great circle distance of the satellite below the radio horizon. The record was taken at the Smyth Research Associates Point Buchon field site on the coast-line near San Luis Obispo, California, with a sea-interferometer system, giving rise to the pattern of maxima and minima above the horizon. Relatively minor tumbling nulls can also be seen superimposed on the interferometer trace.

This work was sponsored by Rome Air Development Center, Air Research and Development Command.

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A Transatlantic Communication Experiment via *Echo* I Satellite

THE article in *Nature* of January 28, p. 268, by Carru, Gendrin and Reyssat, described the reception by the Centre National d'Etude des Télécommunications of 960-Mc./s. signals reflected from the *Echo* I satellite during pass 70.

The signals originated at the Bell Telephone Laboratories' station in Holmdel, New Jersey, U.S.A. The transmitter frequency was measured just before pass 70 and found to be 960·045 Mc./s., which is in good agreement with the value of 960·045053 Mc./s. calculated by Carru *et al.* during reception some 20 min. later.

The 60-ft. diameter transmitting antenna used at Holmdel has a gain of 43·1 ± 0·1 db. instead of the value of 44 db. assumed by Carru *et al.* Transmitter power at the time of reception was 7·5 kW. and was further reduced by the 0·5 db. antenna-transmission line loss to 6·7 kW., which is 0·8 db. less than that assumed by Carru *et al.* Inspection of pointing records for the reception period shows that the Holmdel antenna was aimed to within 0·2° of the satellite, which would add an additional loss of no more than 0·1 db. These factors predict a smaller value for received signal by 1·8 db.; on the other hand, there is no justification for the assumption that the cross-section of the balloon varies with the geometry of the transmission path, as borne out by our own measurements on *Echo* I and the correct theoretical treatment[1]. Thus the 1·3 db. factor used by Carru *et al.* can be omitted, leaving a net loss of 0·5 db., or a predicted received level of −143·0 dbm. This is in good agreement with the value reported, −142 dbm. ± 1 db.

Accurate information regarding the Holmdel transmission is available on request to any independent experimenters who need such information to evaluate their own measurements.

The results of the radio transmission tests supported by the U.S. National Aeronautics and Space Administration and using the *Echo* I satellite over the period August 1960–March 1961 have been evaluated and will be published shortly.

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Bell Telephone Laboratories, Inc.,
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New Jersey.

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WE thank Mr. Jakes for the above information, which corroborates the order of magnitude of our measurements and assumptions. The reference which he points out had only just been published when we submitted our communication (we added it to our ref. 4) and we had not had time to investigate the case of circular polarization, which is not thoroughly examined in Morgan's paper.

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PHYSICS

Apparent Intermediate Supervelocity of Detonation

THE transition from the low to the high detonation velocity in a cylindrical dynamite charge is seen as a rather sharp bend in the streak camera curve. At the transition point the high velocity often starts with an apparent supervelocity which is much greater than the stationary high velocity. The reason is probably that the high velocity is initiated by the low velocity at a point on the axis. Good accordance between observed and calculated values is obtained if it is assumed that the high-velocity detonation sets off from a point a little behind the luminous zone of the low velocity. This accords with the fact that the latter, according to instantaneous photographs, is at the front of the preliminary reaction zone of Selberg and Sjölin[1].

An analogous phenomenon is the initiation of a cylindrical charge by an axial shock-wave. In that case the detonation sets out from a circular, coaxial area on the shock front, the radius of which is smaller than the radius of the charge[2], and the maximum apparent supervelocity goes to infinity.

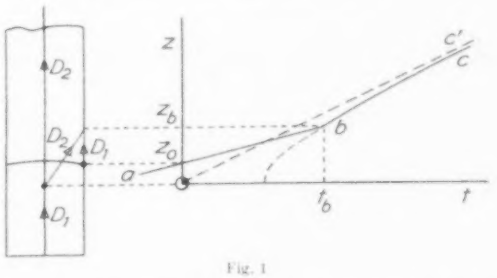

Fig. 1

Fig. 1 gives a schematic picture of the course of events. To the left is shown the cylindrical charge with the front of the low velocity and the starting point of the high velocity when the high velocity starts ($t = 0$). In the time diagram to the right, *abc* shows the course of the luminous front at the envelope surface of the charge. It is obtained from the streak camera photography. *b* is the point where the high-velocity front overtakes the low-velocity front. *Oc'* shows the front of the high-velocity detonation along the axis. The slope of *ab* gives the low velocity D_1, and the derivative of the curve

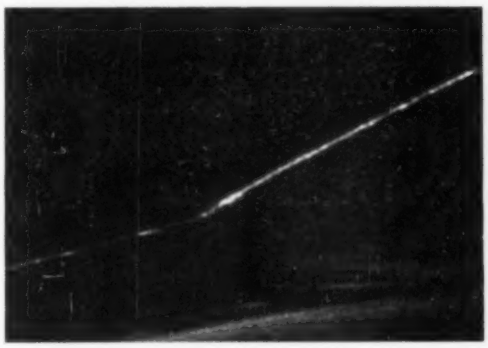

Fig. 2

bc in b gives the maximum apparent supervelocity D_2'. The slope of the asymptote Oc' to the curve bc gives the steady high velocity D_2. If R denotes the radius of the charge, z_b and z_o ordinate values according to Fig. 1, $n = D_2/D_1$ and $m = D_2'/D_2$, we get $z_b = R\sqrt{m^2 - 1}$, $z_o = z_b\,(1 - m/n)$ and $t_b = (z_b - z_o)/D_1$.

Fig. 2 shows a streak camera photo of a charge of gelatinized ammonium dynamite with 35 per cent nitroglycerine/nitroglycol (1 : 1). It was initiated by a donor charge of the same explosive detonating with high velocity. Both charges were in a common tube of 'Plexiglass' with 36 mm. interior and 40 mm. exterior diameter separated by an air gap of 40 mm. The transition point was 27 mm. from the end of the receiver. From Fig. 2 we get: $D_1 = 3{,}030$ m./s., $D_2 = 5{,}760$ m./s. and $D_2' = 7{,}350$ m./s. This gives $n = 1{\cdot}89$, $m = 1{\cdot}28$, $z_b = 22{\cdot}5$ mm., $z_o = 7{\cdot}3$ mm. and $t_b = 5{\cdot}0$ μs.

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Damped Free Oscillations of a Gyroscopic System

The equations of motion of a gyroscopic system consisting of a symmetric rotor of axial moment of inertia C mounted in heavy gimbals are:

$$\left.\begin{aligned} A\ddot{\theta}_1 + c_1\dot{\theta}_1 + Cn\dot{\theta}_2 &= 0 \\ -Cn\dot{\theta}_1 + B\ddot{\theta}_2 + c_2\dot{\theta}_2 &= 0 \end{aligned}\right\} \quad (1)$$

where n is the constant angular velocity of the rotor about its axis; θ_1 and θ_2 are small angles denoting rotations about the outer and inner gimbal axes respectively; c_1 and c_2 are the corresponding coefficients of viscous friction; A is the moment of inertia of the entire system about the outer gimbal axis and B that of the inner gimbal plus rotor about the inner gimbal axis. These equations are based on three principal assumptions: (1) the centres of mass of the rotor and of the gimbals lie at the intersection of the gimbal axes, (2) the axis of the rotor is nearly perpendicular to the axis of the outer gimbal, and (3) the axes of rotation are principal axes of inertia. If there is no friction at the gimbal axes, equations (1) define a free, undamped oscillation in which the rotor axis performs a conical whirl about its central position and the gimbals vibrate at frequency $p = Cn/\sqrt{AB}$.

Now it is well known that friction normally reduces the frequency of free vibrations of an oscillatory mechanical system. The gyroscopic motion defined by equations (1), however, provides an exception to the rule, as may be seen by eliminating θ_2 from (1). This gives

$$\dddot{\theta}_1 + \left(\frac{c_1}{A} + \frac{c_2}{B}\right)\ddot{\theta}_1 + \left(\frac{c_1c_2 + C^2n^2}{AB}\right)\dot{\theta}_1 = 0 \quad (2)$$

Equation (2) represents a damped free oscillation the frequency, p_d, of which is:

$$p_d = \sqrt{\left[\frac{C^2n^2}{AB} - \frac{1}{4}\left(\frac{c_1}{A} - \frac{c_2}{B}\right)^2\right]} \quad (3)$$

Thus the frequency of the damped oscillations will normally be less than that of the undamped oscillations. However, when:

$$\frac{c_1}{A} = \frac{c_2}{B} \quad (4)$$

an exceptional and interesting case occurs, for then p_d is independent of both c_1 and c_2. This condition might easily arise in practice. Even if it were only approximately true, the decrease in frequency due to damping would still be very small: it would, for example, be considerably less than that associated with a conventional system having a single degree of freedom.

It is also interesting to note that if (4) is satisfied, the motion can never be critically damped and must remain oscillatory, even although the damping coefficients and hence the rate of decay of oscillations may become very large.

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CHEMISTRY

Precision and Accuracy in Gas Chromatographic Analysis

The extensive use of gas chromatography to provide quantitative information on the composition of mixtures of organic compounds has prompted an investigation designed to give some indication of the reliability expected. With the exception of the gas density balance, the commonly used detectors do not give a response which can be predicted accurately from the physical or chemical properties of the compounds concerned, so that for highest accuracy calibration is necessary. The development of high-sensitivity detectors has made possible the achievement of high column performance by virtue of the smaller sample loads used, but since reproducible loading becomes more difficult the use of internal standards becomes desirable.

The most widely used high-sensitivity detector is the argon ionization detector devised by Lovelock[1], which combines very high sensitivity with a high degree of stability to changes in rate of flow of gas, temperature and pressure. The linear range of the detector at any given applied voltage is limited but adequate, and a wide dynamic range is achieved by change of applied voltage.

The argon detector in its present form is of robust construction, and when used with suitable power supply and electronic circuitry is capable of giving very accurate and reproducible results. Experience shows that the major cause of detector malfunction is through contamination of the argon carrier gas with either organic or inorganic substances.

Quantitative results obviously rely on the proper functioning of the detector, and a knowledge of the way in which accuracy and reproducibility can be affected is essential.

Organic contamination of the argon entering the detector causes an increase in the background current. Superimposition of a chromatographic peak on this background could result in the observed response extending into the non-linear region. Variation in the level of organic contamination produces a variation in the detector background

current, which appears as an unstable chromatogram baseline. Deposition of organic material derived from stationary phase decomposition on the collecting electrode can result in low detector response. Common sources of organic contamination are cylinder gauge heads, unclean tubing used to convey argon to the column and stationary-phase stripping from the column used.

The process of ionization in the detector is brought about by the transfer of the excitation energy of metastable argon on collision. The formation of sufficient metastable argon for normal detector operation requires the collision of molecular argon with electrons acquiring sufficient energy by acceleration in the applied potential field. The effect of some inorganic contaminants is to prevent the electrons acquiring sufficient energy to create metastable argon; the response of the detector is thereby destroyed. (This effect has been used by Willis[2] to produce a high 'negative' response for permanent gases in a detector fed with an argon stream containing an organic component.) Recent results published by Lovelock[3] show that the greatest effect is produced by water vapour, the sensitivity of the detector being reduced ten-fold by a change in water vapour concentration from about 30 p.p.m. to about 1,000 p.p.m. At less than 30 p.p.m. of water vapour the detector response is constant. The effect of other inorganic contaminants is similar but sets in at higher concentrations. With oxygen, reduction in sensitivity begins at 100 p.p.m. and with nitrogen at 1,000 p.p.m.

It is clear that in order to achieve constant sensitivity and hence reproducible chromatograms it is essential to eliminate or reduce to acceptable limits contamination of the argon supply or to maintain at a constant level deliberately introduced contaminants.

Sources of contamination are listed in Table 1.

Table 1

Site of contamination	*Contaminant*	*Source*	*Effect*
Argon cylinder	Water vapour	Present in cylinder	Low and variable sensitivity
Rubber or plastic argon line	Water vapour, permanent gases	Diffusion through walls of tubing	Low and variable sensitivity
Column	Organic bleed	Unstable stationary phase or operation at too high temperature	High background current, non-linearity, variable sensitivity

Contamination can be avoided by conveying the argon from the cylinder to the column through clean metal tubing and a molecular sieve trap, and by pretreating the column at a temperature in excess of the proposed working temperature.

In order to determine the precision obtainable from a gas chromatograph employing an argon ionization detector, a two-component gas mixture was sampled automatically at regular intervals and chromatographed on a standard Pye argon chromatograph (Fig. 1). Contamination of the argon supply was prevented by passing the argon from the cylinder through a molecular sieve Linde 5A trap and thence to the column in copper tubing which had been cleaned previously by heating to a dull red in a stream of argon. The column used was 10 per cent squalane on 100/120 mesh alumina which had been rendered stable by heating at 100° C. for 24 hr. in a stream of argon. The column temperature was 75° C. and the carrier gas flow-rate 30 ml./min. The sample gas was passed through the automatic sampling valve at about 5 ml./min. to atmosphere, no attempt being made to control the pressure since small variations in the

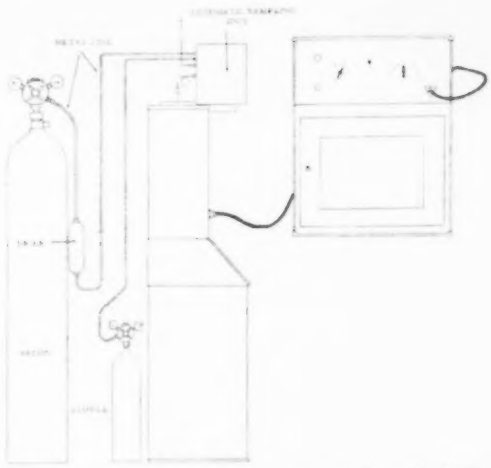

Fig. 1. Apparatus used in the determination of reproducibility

volume injected would not affect the results obtained. Under these conditions the gas mixture consisting of approximately equal amounts of propane and butane was eluted in 8 min. with complete resolution of the two components. A fresh injection of 0·30 ml. of argon containing 1,600 p.p.m. of organic material was made every 10 min. and the run was continued for 4 days. The ratio of the peak heights of the two components was then determined for each injection.

The results obtained (Fig. 2) show an overall spread of about 1 per cent for 110 consecutive determinations. The standard deviation is 0·23 per cent and the 95 per cent confidence limits are ± 0·35 per cent. The base-line deviation was 1·7 per cent full-scale deflexion over 4 days. The sample load added varied by about ± 4 per cent. A second series of injections was carried out, this time using an integrating amplifier to give an

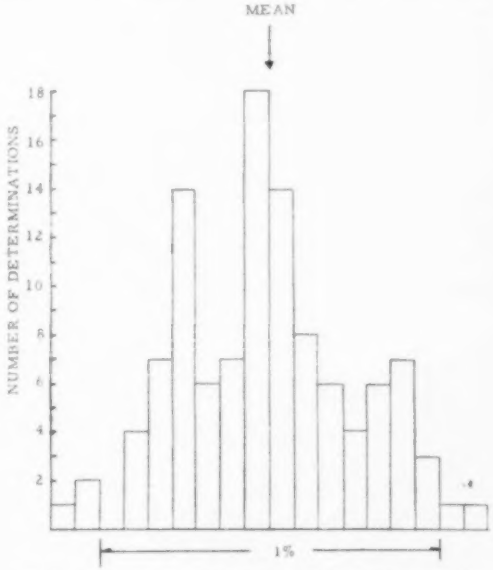

Fig. 2. Variation in peak height ratios from 110 consecutive chromatograms

accurate measurement of peak areas; an overall spread similar to that quoted was obtained.

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An Organo-clay Complex for the Separation of Isomeric Dichlorobenzenes using Gas Chromatography

White[1] has shown that dimethyldioctadecyl ammonium bentonite is particularly suitable as a stationary phase for the chromatographic separation of aromatic and aliphatic compounds, while Hughes, White and Roberts[2] have shown that this material is equally suitable for the separation of isomeric xylenes, toluidines and cresols. Further work by Cowan and White[3] has shown that similar organo-clay complexes are adsorbents for phenols, the adsorbents showing widely differing specificity for the various isomers, and from the data presented the authors propose that the electronic transitions occurring within the sorbate molecules are the main contributory forces governing the extent of adsorption. In consequence, the use of organo-clay complexes for separating isomeric compounds is particularly appropriate and a further example, the separation of dichlorobenzenes, has been investigated and the results obtained compared with those for a conventional liquid stationary phase.

The relative retention volumes for the dichlorobenzenes are given in Table 1 and these are expressed relative to the *para* isomer—in all cases the values are corrected for the dead space of the column. A typical chromatogram is shown in Fig. 1 and this was obtained with a column 200 cm. long × 0·4 cm. bore containing 10 gm. 60–80 mesh 'Celite' as a diluent for 1·0 gm. of dimethyldioctadecyl ammonium bentonite ('Bentone 34', Abbey Chemicals, Ltd.)—the detector was a β-ray ionization unit as supplied by Gas Chromatography, Ltd.

It is noted that using 'Bentone 34' as a stationary phase, a complete resolution of the dichlorobenzenes is obtained whereas with the silicone oil virtually no separation of the *para* and *meta* isomers is effected. Furthermore, even with a capillary column and dinonyl sebacate as a stationary phase complete resolution of these isomers is not possible. It is also noted that, with the solid 'Bentone' stationary phase, symmetrical elution peaks are obtained.

Table 1

	Relative retention volume			
	Silicone oil		'Bentone 34'	
	80° C.	110° C.	80° C.	110° C.
Benzene	0·08	—	0·11	—
Chlorobenzene	0·28	0·37	0·68	0·79
p-Dichlorobenzene	1·00	1·00	1·00	1·00
m-Dichlorobenzene	1·02	1·02	2·23	2·14
o-Dichlorobenzene	1·17	1·12	5·64	4·80
1,2,4-Trichlorobenzene	3·11	2·47	—	16·0
	Specific retention volume (ml.)			
p-Dichlorobenzene	440	161	840	246

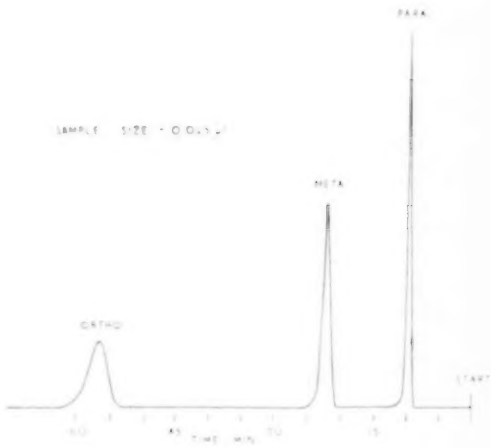

Fig. 1

From the results and those obtained by previous workers, it is suggested that the use of organo-clay complexes as stationary phases in chromatography warrants more detailed investigation. Since interlamellar distances within the clay complex play an important part in the adsorptive properties, and as these distances are governed by the size of the substituting amine ion[4], it is expected that further work will reveal that it is possible to prepare an organo-clay stationary phase of pre-determined resolving characteristics for a specific separation of organic compounds.

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The Possibility of obtaining E.M.F. directly from Acid-Base Reactions: Electrodes of the Third Kind reversible to Alkaline Earth and Other Ions

Some years ago Shedlovsky[1,2] suggested that proton transfer reactions could give rise directly to e.m.f., and apparently confirmed this idea by demonstrating that a glass electrode, coated with lauric acid and barium laurate, acted as a barium electrode. There is a simpler explanation of this result, however: namely, the glass electrode with lauric acid and barium laurate acts as an electrode of the third kind. In a barium chloride solution saturated with these substances, the activities of barium and hydrogen ions must be related by the equation:

$$a_{H} = (k^{2}_{HL}/k_{BaL_2})^{1/2} \cdot a^{1/2}_{Ba}$$

k representing the thermodynamic solubility product. In such solutions the glass electrode, responding to

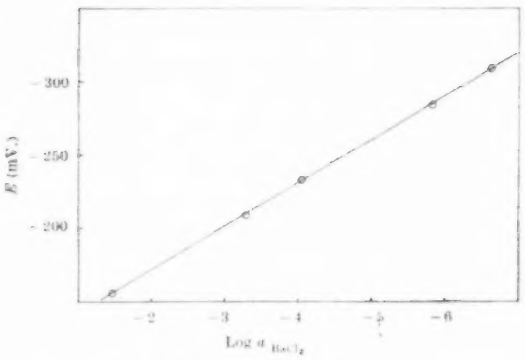

Fig. 1. E.m.f. of the cell: Ag,AgCl/$BaCl_2$ sat. with BaL_2 and HL/glass electrode

hydrogen ion activity in the normal way, would therefore appear to act as a barium electrode.

To check this possibility, solutions of barium chloride ranging in concentration from 0·005 to 0·5 *M* have been shaken with mixtures of solid lauric acid and solid barium laurate at 25° C. and the potential difference between a glass and silver–silver chloride electrode then determined in each of these solutions. The results of these measurements are shown in Table 1 and Fig. 1, in which the straight line has been drawn with the theoretical slope of 29·6 mV. per logarithmic unit. The points referring to 0·5, 0·1 and 0·01 *M* solutions were obtained with one glass electrode and the others with a second glass electrode which was also measured in 0·5 *M* solution. For both electrodes the e.m.f. was set equal to −156 mV. in the latter solution in order to fit the data for the two electrodes together. The measurements are seen to give the expected result. A further check is possible, since the potential difference between the glass and silver chloride electrode in 0·01 *N* hydrochloric acid was also determined. The value was −101·3 mV. compared with the value of −156 mV. in the 0·5-*M* barium chloride solution. Since the e.m.f. of the chain:

$$\mathrm{Ag,AgCl}\Big/\begin{matrix}\mathrm{BaCl_2\ sat.\ with}\\ \mathrm{HL}(s)\ \mathrm{and}\ \mathrm{Ba}L_2(s)\end{matrix}\Big/\begin{matrix}\mathrm{glass}\\ \mathrm{electrode}\end{matrix}\ -\ \begin{matrix}\mathrm{glass}\\ \mathrm{electrode}\end{matrix}\Big/\mathrm{HCl}\Big/\mathrm{AgCl,Ag}$$

should obey the equation:

$$E = (RT/2F)\ln(k^{\circ}_{HL}/k_{BaL_2}) + (RT/2F)\ln(a_{BaCl_2}/a^{2}_{HCl})$$

the ratio $(k^{\circ}_{HL}/k_{BaL_2})$ can be calculated. The value thus obtained was $3{\cdot}9 \times 10^{-9}$. Combining this with the value $k_{BaL_2} = 1{\cdot}2 \times 10^{-11}$, calculated from solubility data[4], one then obtains for the solubility product of lauric acid in water at 25°, $k_{HL} = 2{\cdot}15 \times 10^{-10}$, and hence for the molality of undissociated lauric acid in the saturated solution, $2{\cdot}15 \times 10^{-5}$, if lauric acid is assumed to have a dissociation constant of 10^{-5}. Finally, the solubility of lauric acid at 25° C. is found to be $3{\cdot}6 \times 10^{-5}$ mole kgm.$^{-1}$ water. This may be compared with the value $1{\cdot}9 \times 10^{-5}$ mole l.$^{-1}$ reported by McBain and Eaton[5] from conductivity measurements.

This explanation of Shedlovsky's results implies that the laurate layers on his electrodes were porous or cracked, so that the underlying glass surface was in reality in contact with solution. It also implies that

Table 1

E.m.f. of the cell: Ag,AgCl/$BaCl_2$ sat. with BaL_2 and HL/glass electrode

M ($BaCl_2$)	$\gamma_{\pm}$ (Ref. 3)	E_{298} (mV.)
0·005	0·774	−308·8
0·01	0·716	−283·2
0·05	0·564	−233·1
0·1	0·500	−208·8
0·5	0·397	−156·0

the solutions inside and outside his glass electrodes differed in *p*H, contrary to what he believed. This must have been so in fact, in view of the much smaller buffer capacity of his solutions compared with that of the solids barium laurate and lauric acid, which would therefore determine the equilibrium *p*H of the solution.

It should obviously be possible by this method to obtain electrodes reversible to the other alkaline earth ions, while by varying the acid the list might be extended still further. The method is especially convenient since it makes use of the glass electrode.

Although it is true that the e.m.f. of cells of the type tested does arise directly from acid-base reactions, the detailed mechanism is probably not that suggested by Shedlovsky. Even with the simpler mechanism suggested here, however, acid-base reactions might still be the origin of some bioelectric potentials.

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Spectrum of Vanadium in the Tri-positive Oxidation State (V^{3+}) in Tetrahedral Co-ordination

Vanadium in the tri-positive oxidation state has two unpaired electrons in the 3*d* shell. The interaction of the crystalline electric field with the two *d*-shell electrons has been treated theoretically for fields of various symmetries[1–3]. Most of the information concerning the electronic structure of V^{3+} comes from work on compounds in which the metal ion is co-ordinated to six ligands.

The optical spectra of V^{3+} in alums[4] and in corundum[2,5], where the co-ordination is to six oxygens, agree reasonably well with the calculated energy-level diagrams. The *Dq*-value which fits these data best is 1,800 cm.$^{-1}$. Using the strong field theory, McClure[6] gives the octahedral site preference energy as 12·3 k.cal./mole for oxide lattices.

Since energy-levels are profoundly influenced by a change in co-ordination number, it is of interest to learn more about four co-ordinate V^{3+} (ref. 7). We have now obtained the spectrum of V^{3+} substituted for Al^{3+} in the $CsAlCl_4$ lattice (Fig. 1). Single crystals of this material were grown containing a few tenths per cent of V^{3+}. They are blue in colour. Tetrahedral $AlCl_4^-$ ions have been shown to exist as structural units in the $NaAlCl_4$ lattice[8] and, presumably, are present also in the $CsAlCl_4$ lattice.

The room temperature spectrum is characterized by four bands with maxima at 15,000; 10,250; 9,400; and 8,250 cm.$^{-1}$. The total oscillator strength

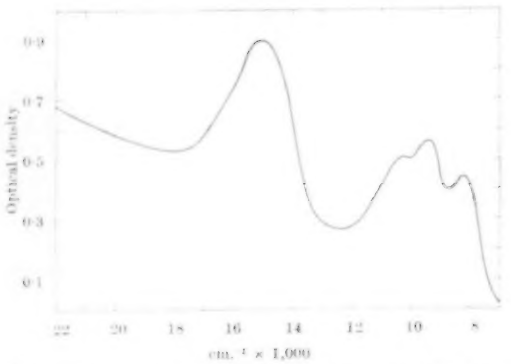

Fig. 1. Absorption spectrum of V^{3+} in $CsAlCl_4$ at room temperature

in the region 17,000–7,000 cm.$^{-1}$ is about 10^{-2}. The bands overlap and are not symmetrical. They can be expected to show additional structure at low temperatures. Liehr and Ballhausen's energy-level diagram, based on pure crystal field theory calculations for a d^2 system in a tetrahedral field[1], gives two $^3T_1$ levels at 16,000 and 9,000 cm.$^{-1}$ and a $^3T_2$ level at 5,000 cm.$^{-1}$ for $Dq = -500$ cm.$^{-1}$.

Tripositive vanadium can also be situated in an octahedral chloride ion environment. This would appear to be the case, for example, in molten lithium chloride–potassium chloride eutectic[9,10]. In this solvent, two bands are found at 18,000 and 11,000 cm.$^{-1}$ corresponding to transitions from the $^3T_1$ ground-state to $^3T_1$ and $^3T_2$ excited states, respectively. Good agreement with the theoretical energy-level diagram is obtained with $Dq = 1{,}200$ cm.$^{-1}$. Using Dq-values of -500 and 1,200 cm.$^{-1}$ for tetrahedral and octahedral environments respectively, one finds the octahedral site preference energy for V^{3+} in chloride lattices to be 10·5 k.cal. on the strong field model.

Spectral intensity calculations on $CuCl_4^{2-}$ and $CoCl_4^{2-}$ ions led Ballhausen and Liehr[11] to postulate that tetrahedral complexes display a certain degree of covalency. It would appear from the present work that covalent bonding in VCl_4^- affects not only the intensity of the spectrum but also the energy-level structure of the ion. An extension of the theory, which would include covalency effects, will undoubtedly be required in order to obtain better agreement with the experimentally observed spectrum.

The technique of isomorphous substitution of a transition metal ion in a colourless host lattice was applied in the present case to obtain a particular configuration difficult to produce by other means. Other examples of host lattice configuration stabilization have been reported for tetrahedral Co^{2+} and Ni^{2+} in oxide[6] and chloride[11] lattices. The phenomenon is being put to use in work on a number of other transition metal ions.

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Structure of Polynuclear Cobalt Complexes

It is known that molecular oxygen will react with the hexamminecobalt(II)-ion, whereby different kinds of complexes are formed. Among these complexes, the following types are described in the literature:

$$[(NH_3)_5Co{-}O_2{-}Co(NH_3)_5]X_5$$

$$[(NH_3)_4Co(O_2)(NH_2)Co(NH_3)_4]X_4$$

$$[(NH_3)_4Co(OH)(O_2)(NH_2)Co(NH_3)_4]X_5$$

Lately the bonding in these compounds has been much discussed, and it therefore appears to be of considerable interest to establish their structures. Work on the crystal structures of compounds belonging to the first of the above-mentioned types have been going on at this institute for several years. The following compounds have been investigated by the usual X-ray methods:

$$[(NH_3)_5Co{-}O_2{-}Co(NH_3)_5](NO_3)_5$$

$$[(NH_3)_5Co{-}O_2{-}Co(NH_3)_5](NO_3)_5.HF_2.(H_2O)_2$$

The nitrate was found to have tetragonal symmetry, corresponding to the space group $P4_2nm$ (No. 102). The dimensions of the elementary cell are $a = b = 11{\cdot}94$ Å. and $c = 8{\cdot}06$ Å. The cell contains two formula units. Parameter values for all the atoms with the exception of the hydrogens have been determined by a three-dimensional Fourier summation (Table 1). The reliability index R is calculated to be 0·20.

Table 1. Parameter Values for $[(NH_3)_5Co{-}O_2{-}Co(NH_3)_5](NO_3)_5$. Space Group $P4_2nm$

Atom	Position	Number	x	y	z
Co	c	4	0·134	0·134	0·000
NH_3	d	8	0·213	0·054	0·181
NH_3	d	8	0·054	0·213	0·814
NH_3	c	4	0·250	0·250	0·012
O	c	4	0·457	0·457	0·512
N	a	2	0·500	0·500	0·988
N	c	4	0·265	0·265	0·550
N	b	4	0·500	0·000	0·000
O	a	2	0·500	0·500	0·138
O	c	4	0·438	0·438	0·913
O	c	4	0·192	0·192	0·500
O	c	4	0·290	0·290	0·407
O	c	4	0·295	0·295	0·090
O	b	4	rotating, $r = 1{\cdot}2$ Å.		
O	b	4			

The constitution of the cation complex can be seen from Fig. 1. It will be noted that the axis of the peroxide group is perpendicular to a line connecting the two cobalt atoms, as predicted by Vlček[1].

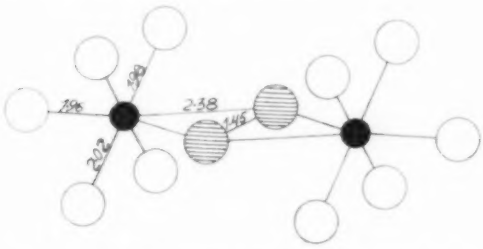

Fig. 1. Configuration of the ion $[(NH_3)_4Co{-}O_2{-}Co(NH_3)_4]^{5+}$. Shaded, O; white, NH_3; black, Co

The compound containing the fluoride as well as the nitrate anion has been prepared by treating the nitrate with a concentrated aqueous fluoric acid solution. The following crystallographic data have been obtained for this compound: space group *Pbca* (No. 61) and unit cell dimensions $a = 13{\cdot}14$ Å., $b = 12{\cdot}21$ Å. and $c = 14{\cdot}14$ Å. The unit cell contains four formula units.

As expected, the compound is composed of complex groups, as indicated in Fig. 1, in addition to water, nitrate groups and hydrogen difluoride groups. The atomic parameter values obtained so far give an *R*-factor of 0·34. A least-square refinement of the structure has therefore been undertaken.

A complete report of both these and related structure investigations will be published elsewhere.

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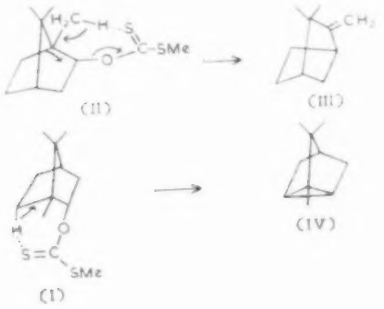
Pyrolysis of Esters of Borneol and *iso*Borneol

IT is generally believed that esters pyrolyse to give the products of *cis* elimination in a six-membered cyclic transition state[1]. Recently, however, products corresponding to a *trans* elimination have been shown to be formed by the pyrolysis of methyl xanthates of some substituted *cyclo*hexanols[2]. The pyrolyses of xanthates and acetates of 1-alkyl*cyclo*hexanols give predominantly the more stable endocyclic olefins[3], and both *cis* and *trans* elimination have been observed in pyrolyses of chlorosulphites[2], and sulphoxides[4].



Tschugaeff isolated bornylene, containing some tricyclene, from the pyrolysis of bornyl methyl xanthate[5]. Huckel has isolated camphene from the pyrolysis of *iso*bornyl xanthate[6], and camphene has been shown to be a pyrolysis product of bornyl sulphites[7]. We have examined the pyrolysis products of methyl xanthates and benzoates of borneol and *iso*borneol; cf. (I) and (II), respectively. The methylxanthates were decomposed using a bath at 300°, at which temperature the decomposition was almost instantaneous; the benzoates decomposed comparatively slowly when the bath was at 350°. The products distilled off and were analysed and separated by gas-liquid chromatography (Table 1).

Table 1. COMPOSITION AND CONFIGURATION OF PYROLYSIS PRODUCTS. (Figures in parentheses are percentage retention of configuration)

	Bornylene (per cent)	Tricyclene (per cent)	Camphene (per cent)
Bornyl methyl xanthate	70 (100)	13·5	16·5 (~ 30)
*Iso*bornyl methyl xanthate	38·5 (92)	—	61·5 (~ 100)
Bornyl benzoate	24·5 (97)	21·5	54 (~ 30)
*Iso*bornyl benzoate	—	13	87 (~ 30)

The bornylene was probably formed through the classic *cis* elimination mechanism[1], but this mechanism cannot explain the formation of camphene (III) and tricyclene (IV). Maccoll[8] and co-workers have emphasized the similarity between the gas-phase pyrolyses of alkyl halides and their unimolecular solvolyses, and emphasize the importance of charge separation in the transition state[2]. Following these ideas, we can explain the composition of the product by assuming that the part of the reaction which gives camphene and tricyclene is 'quasi-heterolytic'[8], because the initial elimination product of the solvolyses of bornyl and *iso*bornyl chlorides is always camphene. The amount of camphene is greater in the pyrolyses of the *iso*bornyl esters, and *iso*bornyl compounds form carbonium ions much more readily than do bornyl compounds. Similarly, carbonium ions should be generated much more readily by benzoates than by xanthates, and the former always give more camphene and less bornylene; although the temperature difference may make this comparison misleading.

The formation of camphene of high optical purity from *iso*bornyl methyl xanthate suggests that there is a seven-membered cyclic transition state, in which breaking of a C—H bond is synchronous with the migration of C—C bond electrons, and separation of the leaving group, but the formation of partially racemic camphene from the other esters shows that for them the decomposition must be step-wise, with loss of asymmetry at some stage. A similar synchronous mechanism can be written for the formation of tricyclene (IV).

As might be expected, the bornylene is more than 90 per cent optically pure, and bornylene and camphene and reactants have the same configuration. Because in these pyrolyses we observe products typical of a Wagner–Meerwein rearrangement, we have stressed the analogy with carbonium-ion chemistry, but our cyclic mechanisms could be considered to have some homolytic character, and it is also possible that some 1 : 1-elimination might lead to a carbene intermediate.

We are grateful to Dr. D. J. Cram for interesting discussions.

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BIOCHEMISTRY

Hydrolysis of Paraoxon in Mammalian Blood

Several publications have indicated that in the detoxication of paraoxon (diethyl *p*-nitrophenyl phosphate, '*E*600,' 'Mintacol') the mammalian blood serum might be of importance[1-3]. Aldridge[4] was first to describe the existence of an *A* esterase (aryl-, aromatic esterase) which hydrolyses paraoxon. This enzyme occurs in the sera of various species[4], but the extent of its involvement in the metabolism of paraoxon is not yet clear[5,6]. Among other properties, the arylesterase cleaves phenyl acetate[7], and it has been shown with this substrate that the enzyme requires the presence of calcium for activity[8,9]. The arylesterase is activated by calcium and inhibited by sodium ethylenediaminetetraacetate and numerous other compounds[8-11]. In human blood plasma it occurs in fraction IV–1[12,13]. Since preliminary experiments indicated that in addition to this arylesterase, at least one more factor might be responsible for the hydrolysis of paraoxon in blood serum or plasma, we undertook the present investigations.

The cleavage of paraoxon was followed in a Cary recording spectrophotometer, by determining the amount of *p*-nitrophenol liberated at a wave-length of 4000 Å., or in some of the experiments at 3470 Å. The temperature was kept constant at 37° C., the *p*H at 7·9. The 0·1 *M tris*(hydroxymethyl)aminomethane buffer was $4{\cdot}5 \times 10^{-3}$ *M* in substrate and 2·4 per cent in propylene glycol. The results were calculated from the initial rates of hydrolysis.

Fig. 1 summarizes some of the results. As shown in Fig. 1*A*, fresh pooled human serum hydrolyses paraoxon at an appreciable rate. This activity was inhibited only 86 per cent by a 0·01 *M* concentration of ethylenediaminetetraacetate. Since the cleavage of paraoxon by purified human arylesterase (fraction IV–1) was completely abolished by a concentration of ethylenediaminetetraacetate 20 times lower (*D*), clearly the residual activity in the serum was not due

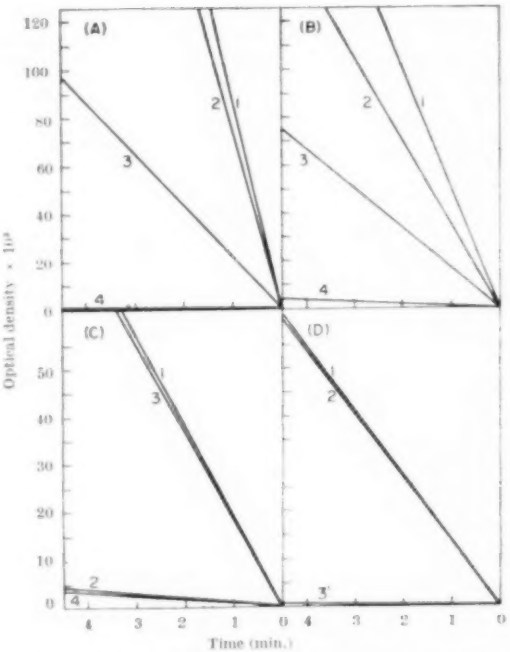

Fig. 1. Inhibition of the hydrolysis of paraoxon in human blood serum (*A*) and plasma fractions (*B*, *C*, *D*). Dilutions: *A*, pooled serum, 1 : 20 v/v; *B* fractions IV–1, 1 mgm./ml. + V, 4 mgm./ml. w/v; *C*, fraction V, 4 mgm./ml.; *D*, fraction IV–1, 0·5 mgm./ml. (1) control; (2) aluminon 1×10^{-3} *M*; (3) ethylenediaminetetraacetate 1×10^{-3} *M*; (3') same 5×10^{-4} *M*; (4) aluminon 1×10^{-3} *M* + ethylenediaminetetraacetate 1×10^{-3} *M*

to arylesterase, but to something else. The splitting of paraoxon, however, was completely blocked when the serum, in addition to ethylenediaminetetraacetate, contained 10^{-3} *M* aurin tricarboxylic acid ammonium salt (aluminon) (*A*). While looking for the source of the activity resistant to ethylenediaminetetraacetate we found that human albumin (fraction V or crystallized) also hydrolyses paraoxon, and indeed this hydrolysis is inhibited by aluminon (*C*). Even after 18 hr. of incubation ethylenediaminetetraacetate had no effect on the albumin. On the other hand, the enzymic hydrolysis of paraoxon by fraction IV–1, as indicated above, was inhibited by ethylenediaminetetraacetate, and unaffected by aluminon (*D*). When plasma arylesterase (fraction IV–1) and albumin (fraction V) were mixed (*B*) the results with selective inhibitors were similar to those with normal serum. However, in the presence of albumin the activity of fraction IV–1 is somewhat higher than expected.

The behaviour of albumin with paraoxon was further explored with the help of various agents. Albumin (or a factor in albumin) was inhibited to about 50 per cent (I_{50}) by 2×10^{-4} *M* aluminon. This inhibition was not reversed by overnight dialysis. Lineweaver–Burk-type plots[14] showed a non-competitive inhibition. Some other enzyme inhibitors or activators such as oxalic acid (0·01 *M*) or mercuric chloride (5×10^{-4} *M*) nevertheless gave negative results. Since the preparations used were not activated by Sr^{2+} and Ba^{2+}, the presence of a phosphoryl phosphatase[15] is unlikely. But albumin was definitely inhibited by sodium, potassium or lithium chloride. The I_{50} values were roughly 0·5 *M*. Albumin was more

sensitive to monovalent anions than to cations; the I_{50} of sodium bromide is about 0·1 *M*; that of sodium iodide, 0·01 *M*.

Fluoride was not tried as an inhibitor because we had seen that 10^{-3} *M* potassium or sodium fluoride catalyses the hydrolysis of paraoxon at a relatively high rate. The rate of this reaction was similar to the one catalysed by albumin in the concentration shown in Fig. 1,*C*. Other metals and organic compounds, among them the cholinesterase reactivator pyridine-2-aldoxime methiodide (2-PAM), used frequently in paraoxon poisoning[16,17] had an analogous effect. (The subject was recently reviewed extensively by O'Brien[18].) This catalytic activity at a 1×10^{-3} *M* concentration decreased in the following order: 2-PAM, sodium fluoride, *p*-chloromercuriphenylsulphonic acid, zinc sulphate, cadmium sulphate, manganese chloride, cobalt chloride, mercuric chloride. The zinc-ethylenediaminetetraacetate was not active.

Reagents and procedures known to denature proteins also destroyed the activity of albumin. For example, albumin became inactive after heating it at 70° C. for 10 min. Furthermore, 4 *M* urea abolished 80 per cent of the activity in 1 hr. Calcium chloride protected the protein; in the presence of 0·01 *M* calcium chloride only 40 per cent was inactivated. In contrast to the results with arylesterase[19], lanthanum chloride was less effective than calcium chloride. Other alkaline earth salts (magnesium chloride, strontium chloride) also protected the albumin, but less than calcium chloride.

When the investigations were expanded to serum proteins of other mammals, swine serum was found to behave like human serum (see Fig. 1,*A*). Serum albumin of other animals also destroyed paraoxon. The relative activity of the various albumin fractions decreased in the following order: rabbit, human, porcine, bovine, equine. Under our conditions, 100 mgm. of human albumin hydrolysed 2·4 μ*M* paraoxon per hour. These albumins were also inhibited to a varying extent by aluminon but unaffected by ethylenediaminotetraacetate, etc. On the other hand, ethylenediaminetetraacetate blocked partially or completely the hydrolysis of paraoxon in the sera of pig, horse, rabbit, guinea pig, and sheep.

Lactalbumin, lysozyme, and human plasma cholinesterase (fraction IV–6–3) hydrolysed paraoxon to a negligible extent. Like arylesterase, albumin also splits phenyl acetate. While the relative ratio of hydrolysis-rates of phenyl acetate to paraoxon by fraction IV–1 was about 600 : 1 in the two systems employed, it became 1 : 1 with albumin as source of 'enzyme'.

In preliminary studies with the Spinco model *E* analytical ultracentrifuge fraction V gave a single peak, but in starch-gel electrophoresis human albumin from various sources showed contamination by globulin. However, in experiments where the sample had been pre-treated with the inhibitor aluminon, the albumin band migrated at a higher speed in front of the field.

The similarities and dissimilarities between the hydrolysis of paraoxon and other 'substrates' of albumin, for example, β-naphthylacetate, β-carbonaphthoxycholine[18], carbamates[12,20], di*iso*propoxy phosphoryl fluoride[21], indophenyl acetate[22] and other details are discussed elsewhere.

Our present experiments indicate that mammalian serum albumin (or a factor in it) hydrolyses paraoxon at an appreciable rate. Selective inhibitors can distinguish its activity from that of serum arylesterase.

The kind co-operation of Drs. W. Jensen, R. Rice and M. Westerman in some of the experiments is gratefully acknowledged.

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Precautions in the Use of Ferri- or Ferrocyanide for the Study of Hæmoproteins

POTASSIUM ferri- and ferro-cyanide are extensively used as oxidizing and reducing reagents respectively, or as buffer systems in the study of the oxidation-reduction potentials of hæmoproteins and other biological compounds. It was shown, however, by Schönbein and some other workers, especially Baudisch and Bass[1], that these reagents easily undergo photodecomposition accompanied by the liberation of a certain amount of cyanide. Solutions of these reagents must therefore be not only freshly prepared, but also well protected from light, especially when used for the study of hæmoproteins which may have high affinities for cyanide, forming with it well-defined complexes.

In this respect it may be interesting to recall a red compound described by Bock[2] as 'photomethæmoglobin', which he obtained from methæmoglobin exposed to strong light. He also recorded the absorption spectrum of this derivative, which differed markedly from those of methæmoglobin and hæmoglobin. Bock's 'photomethæmoglobin' was re-examined by Haldane[3], who identified it as the cyanmethæmoglobin compound discovered and well described by Kobert[4]. Cyanide, according to Haldane, originated in Bock's experiments from the photodecomposition of ferricyanide present in his solution of methæmoglobin when it was exposed to light. Haldane[3], being unaware of the fact that the light-

sensitivity of ferricyanide had already been recorded before, carried out some interesting experiments on this subject. Thus, on treating methæmoglobin in the dark with a solution of ferricyanide previously exposed to light, Bock's 'photomethæmoglobin' was immediately obtained, and was indistinguishable from cyanmethæmoglobin formed by treating methæmoglobin with cyanide. Haldane's conclusion as to the nature of 'photomethæmoglobin' was corroborated by Zeynek[5].

On several occasions in the course of recent experiments, I have observed the formation of the cyanferriperoxidase complex during spectroscopic examinations of samples of pure peroxidase treated with ferri- or ferro-cyanide solutions freshly prepared, but not protected from light. These experiments suggest that if a hæmoprotein compound, treated with ferri- or ferro-cyanide solutions, shows certain changes in its absorption spectrum, or in some of its other properties, which cannot be accounted for by simple oxidation or reduction reactions, it is advisable to compare the derivative thus obtained with the same hæmoprotein solution treated with different concentrations of cyanide.

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A New Technique of Chromatography and Ionophoresis on Ion-exchange Paper. Application to Separation of Barbiturate, Salicylate, Acetophenetidin and *p*-Acetylaminophenol

In a previous communication, we[1] showed that a mixture of salicylate, barbiturate, and acetophenetidin could be separated by a combination of chromatography and ionophoresis on a sheet of cellulosic anion-exchanger.

According to Stewart and Stolman[2], a major metabolite of acetophenetidin in the human body is *p*-acetylaminophenol. When *p*-acetylaminophenol is subjected to chromatography on Whatman *DE*20 ion-exchange paper, it moves at approximately the same speed as phenobarbitone, so that a mixture of these two compounds is not resolved. However, if the paper is now subjected to ionophoresis, the *p*-acetylaminophenol moves more slowly than the barbiturate. This means that, by using our new technique[1] of chromatography and ionophoresis on ion-exchange paper, it is possible to obtain complete resolution of a mixture of salicylate, phenobarbitone, acetophenetidin and *p*-acetylaminophenol. The results are illustrated in Fig. 1.

It also has been observed that when the wet sheet (following ionophoresis) is viewed in the light from a mercury-vapour lamp emitting radiation at 2,537 Å., the *p*-acetylaminophenol shows up as a dark purple absorbing spot. However, after the paper has dried, the spot shows a very light blue fluorescence when viewed in the ultra-violet light. This phenomenon is observed when only *p*-acetylaminophenol is present. It occurs following chromatography in dilute

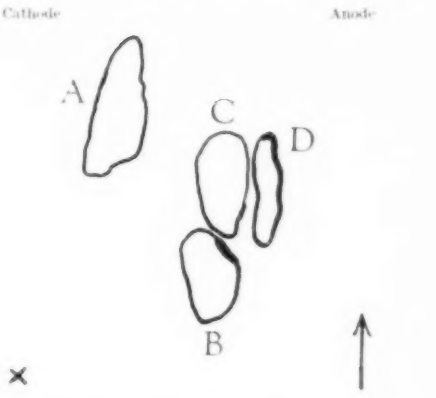

Fig. 1. Chromatography in 0·2 *N* ammonia (15 min.) followed by ionophoresis in 0·2 *N* ammonia (60 min.; constant current, 5 m.amp.; initial voltage, 250 V.) of a mixture of acetophenetidin (*A*), salicylate (*B*), *p*-acetylaminophenol (*C*) and phenobarbitone (*D*). Arrow indicates direction of ascending solvent-flow during chromatography; mixture applied at ×

ammonia solution, but not when applied to the paper without ammonia treatment. Hence, the final dried sheet when examined in ultra-violet light shows the pale-blue fluorescent spot of *p*-acetylaminophenol differentiated quite clearly from the faster moving and dark purple absorbing spot of phenobarbitone.

The chromatography separation takes about 15 min., ionophoresis about 1 hr. 0·2 *N* ammonia solution is used as 'solvent'.

A full account of these procedures will be published elsewhere.

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Isolation of Beta-Alanine from *Iris tingitana* (var. Wedgewood)

Beta-alanine has often been reported (for example, Hulme and Arthington[1]) in plants on the basis of chromatographic evidence and is now considered to be a common plant constituent[2].

Virtanen and Laine[3] isolated beta-alanine from the root nodule bacteria of peas, but there is no published report of the isolation of beta-alanine from higher plants. In the process of isolating beta-amino*iso*-butyric acid from iris bulbs[4], beta-alanine has been obtained in crystalline form and characterized by classical physical and chemical methods.

Beta-alanine and beta-amino*iso*butyric acid were separated from the other neutral amino-acids in the 80 per cent ethanol extract of iris bulbs (45 kgm.) on 'Dowex 1' in the salt form[5]. The two beta amino-acids were separated from each other by chromatography with *n*-butanol/methanol/water (2 : 2 : 1) on a paper roll. Final purification was accomplished by crystallization from aqueous ethanol, resulting in 300 mgm. of material. Quantitative analysis of an extract of a different sample of Wedgewood iris resulted in a value of 0·045 μmole of beta-alanine per gm. of tissue fresh weight. The elemental analysis of the isolated material was 40·5 C, 7·93 H and 15·7 per cent N

(theoretical values for beta-alanine are 40·3 C, 8·15 H and 15·6 per cent N). The infra-red spectrum of the isolated material in a potassium bromide disk was identical with that of authentic beta-alanine. The iris amino-acid co-chromatographed with beta-alanine in phenol/water (8 : 3), butanol/acetic acid/water (9 : 1 : 2·5) and *n*-butanol/methanol/water (2 : 2 : 1).

The 2,4-dinitrophenyl derivatives of the isolate and authentic beta-alanine were prepared by Levy's method[6]. After several recrystallizations from 95 per cent ethanol, the derivatives of the isolated and synthetic amino-acids melted at 146–147° C. (uncorrected). A mixed melting point of 146–147° C. was observed. Co-chromatography of the two derivatives in Levy's solvent system produced no separation.

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Possible Role of Nucleopeptides in Protein Biosynthesis

WE have reported on the isolation of nucleopeptides from guinea pig liver[1]. Further work[2,3] has revealed that these compounds were oligonucleotides combined with various peptides containing more than ten amino-acids. Steinberg *et al.*[4] have isolated some compounds of similar kind from rat kidney and liver, as well as from rabbit liver.

This communication presents some results concerning nucleopeptide biosynthesis within a cell-free system, as well as their incorporation into protein.

Guinea pigs were used for experiments. The nucleopeptide synthesis was carried out by a method identical with that applied for protein biosynthesis *in vitro*. The mixture composition was that described under Fig. 2, the only difference being that in this experiment 1 ml. of the mixture contained, instead of nucleopeptides, 0·66 μc. of L-glutamate, 0·66 μc. of L-aspartate, 0·66 μc. of L-arginine and 0·3 mgm. of each of the twenty various non-radioactive L-amino-acids; the radioactive ones just mentioned were omitted. One-half of this mixture was sampled at the beginning of the experiment and saturated with solid ammonium sulphate. The other half was incubated at 37° for 20 min., then treated with ammonium sulphate in the same manner. Nucleopeptides were isolated from these solutions by means of ethanol according to the procedure described in ref. 1. The residue obtained, after removal of ethanol, was eluted with acidified acetone (0·4 ml. of 1 *N* hydrochloric acid per 10 ml. of acetone), transferred on strips of Whatman No. 1 paper (5 × 57 cm.) and electrophoresis was carried out in the Markham and Smith apparatus[5]. The applied conditions were: ammonium acetate buffer 0·08 *M*, *p*H 5·0, potential gradient 50 V./cm., temperature 10–15°, and time 2 hr. The material examined was separated into three fractions visible in ultra-violet light and moving towards the cathode. The control test showed that these fractions did not contain free glutamate at all and neither aspartate nor arginine. The fractions were excised, eluted with 0·01 *N* hydrochloric acid, concentrated by evaporation and chromatographed within the solvent system containing butanol–acetic acid–water (4 : 1 : 5). The chromatography of radioactive glutamate, aspartate and arginine was performed under identical conditions. The photograph of the chromatogram was then taken in ultra-violet light and autoradiographed for 6 weeks (Fig. 1). The darkened areas of the autoradiograph corresponded to spots in the picture taken in ultra-violet light, although some spots showing absorption at 260 mμ did not contain any radioactivity. The paper was then sprayed with 0·5 *N* salt-free hydroxylamine and dried in air. After treatment with acidified ferric chloride some pink-brown spots arose which indicated the presence of hydroxamic acids. They corresponded in their localization to the spots found in the picture taken in ultra-violet light, as well as to the darkened areas of the autoradiogram. The spots showing high radioactivity were excised, eluted with 0·01 *N* hydrochloric acid and the eluate hydrolysed with 6 *N* hydrochloric acid for 16 hr. at 105°. Then hydrochloric acid was evaporated, iron removed with ammonium hydroxide, the residue chromatographed, as described, and the chromatogram developed with ninhydrin. Three to seven spots were found. The spots corresponding to glutamate, aspartate and to arginine were excised and their radioactivity was recorded.

Experiments were undertaken afterwards to establish whether the peptide part of nucleopeptides might

Fig. 1. The autoradiographed chromatogram of the nucleopeptides obtained *in vitro* in the presence of carbon-14 labelled glutamate, aspartate and arginine, as well as that of the standard amino-acids. 1, 2 and 3 are fractions of nucleopeptides after incubation and electrophoresis; O, before incubation

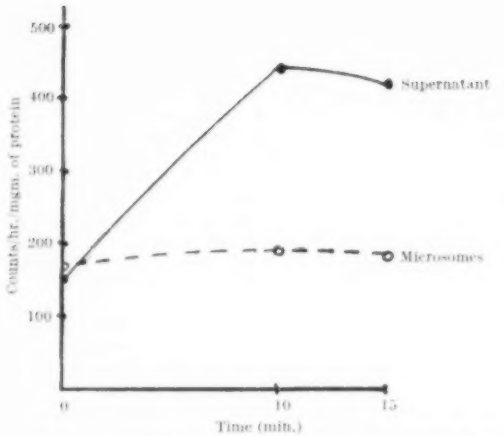

Fig. 2. Incorporation of nucleopeptides into proteins within a cell-free system. Incubation mixture contained in 1 ml.: 12 mgm. of the guinea pig liver microsomal protein (obtained in 0·25 *M* sucrose between 10,000*g* and 40,000*g*), 5·6 mgm. of the *p*H 5 enzymes from the supernatant at 40,000*g*, 0·58 mgm. of ATP (potassium), 4·4 mgm. of potassium chloride, 0·12 mgm. of $MgCl_2$, 4·6 mgm. of phosphocreatine (sodium), 0·3 mgm. of the phosphocreatine kinase, 0·07 mgm. of GTP ($2Na.2H_2O$) ^{14}C-nucleopeptides, 3,200 c.p.m. Components were dissolved in 0·1 *M tris* buffer, *p*H 7·5. Samples for the radioactivity measurement were diluted with a threefold volume of 0·25 *M* sucrose and centrifuged at 40,000*g*

be incorporated into protein when preparations for synthesizing protein *in vitro* were applied. Radioactive nucleopeptides were derived from the liver of a guinea pig which had been injected into the heart with carbon-14 labelled glutamate, aspartate and arginine at doses of 45 μc./kgm. body-weight. The animal was killed by decapitation 3 min. after injection and nucleopeptides were isolated[1,2], the free radioactive amino-acids being removed by means of paper electrophoresis as described. The nucleopeptides formed *in vivo* eluted from electropherograms were added to the system for synthesizing protein *in vitro*. Then the radioactivity of protein was measured in microsomes as well as in the supernatant after centrifugation at 40,000*g*. The purification of proteins for this estimation was carried out according to the commonly applied procedure[3]. The radioactivity was measured with an end window Geiger–Müller counter. Fig. 2 shows that radioactivity appears mainly in the supernatant proteins, whereas its incorporation into microsomes is considerably less.

Our experiments prove that nucleopeptides are formed in the system for synthesizing protein *in vitro* and it seems that they participate in protein biosynthesis.

Details of these investigations will be published in *Acta Biochimica Polonica*.

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Configuration of the 6-Hydroxyl Group in Phenolic Steroids

During recent years reports from various laboratories have indicated that phenolic steroids substituted at C_6 may have biological significance. Thus, Mueller and Rumney[1] provided evidence for the conversion of radioactive œstradiol-17β to 6-hydroxyœstradiol-17β by mouse liver microsomes *in vitro*. Furthermore, 6-hydroxyœstradiol-17β has been isolated as a metabolite after incubation of œstradiol-17β with slices of rat liver[2] and human fœtal liver[3]. Bush *et al.*[4] detected 6-hydroxyœstradiol-17β in the follicular fluid of the mare, and Marrian[5] reported on the isolation of a new Kober chromogen (*KC*–6*B*) which appears to be identical with a 6-hydroxyœstrone.

The 6-hydroxyœstradiol-17β which served as a reference compound in this work was obtained by borohydride reduction of 6-oxo-œstradiol-17β[6]. Wintersteiner and Moore[6] have given reasons for believing that the 6-hydroxyl group thus formed may have a quasi-equatorial configuration; accordingly the compound was provisionally designated as 6'α'-hydroxyœstradiol-17β.

There seemed to exist various possibilities of obtaining more decisive configurational evidence, one of which involved the biological aromatization of 6α- and 6β-hydroxylated C_{19}-steroids to the corresponding phenolic steroids. After preliminary experiments it was decided to employ the aromatizing enzyme preparation from human placenta which has been shown by Ryan[7] to be most efficient in converting C_{19}-steroids to C_{18}-steroids. The investigation of the problem necessitated a paper chromatographic system for the separation of the two epimeric 6-hydroxyœstradiols. Both compounds are easily separated from each other in the system formamide/chloroform (5): ethyl acetate (1), the 'α'-epimer (formed by reduction of 6-oxo-œstradiol-17β with sodium borohydride[6]) travelling faster than the 'β'-epimer (formed by catalytic reduction of 6-oxo-œstradiol-17β with platinum oxide in ethanol[6]).

The incubation of 6α-hydroxy-Δ^4-androstene-3.17-dione with the 10,000*g* supernatant fraction of human placenta homogenate in the presence of adenosine triphosphate and diphosphopyridine nucleotide resulted in the formation of a phenolic metabolite which had the same R_F value as 6'α'-hydroxyœstrone[8] in the system formamide/chloroform. After reduction of the 17-oxo-group with sodium borohydride and subsequent chromatography in the formamide/chloroform-ethyl acetate system the substance showed the same mobility (14·7 cm./14 hr.) as the 6-hydroxyœstradiol-17β provisionally designated by Wintersteiner and Moore[6] as the 6 'α'-compound. When 6β-hydroxy-Δ^4-androstene-3.17-dione was incubated with the placental enzyme a phenolic metabolite was formed having a similar R_F value to 6'β'-hydroxyœstrone in the system formamide/chloroform. Reduction with sodium borohydride yielded a substance which on chromatography in the system formamide/chloroform-ethyl acetate showed the same mobility (12·8 cm./14 hr.) as the 6-hydroxyœstradiol-17β provisionally designated as the 6'β'-compound. After elution from the paper the material was acetylated and subjected to sublimation under atmospheric pressure. The melting point of the crystals (175–177°) was identical with that of authentic 6'β'-hydroxyœstradiol-17β-triacetate. An additional experiment was carried out with 6β-hydroxy-19-nor-testosterone. The phenolic substance obtained after incubation

of this steroid with the placental enzyme showed the same mobility in the formamide/chloroform-ethyl acetate system as 6β'-hydroxyœstradiol-17β. By control experiments, the possibility was excluded that epimerization or oxido-reduction of the 6-hydroxyl groups in the neutral and phenolic steroids had occurred during incubation with the aromatizing enzyme.

Since the configuration of the 6-hydroxyl groups in neutral steroids[9] is well established, the experiments reported here now permit the definite assignment of configurations to the two epimeric 6-hydroxyœstradiols. The 6-hydroxyœstradiol-17β which results from reduction of the 6-oxo group with sodium borohydride is assigned the 6α-configuration, whereas the other epimer which is formed by catalytic reduction with platinum oxide has the 6β-configuration.

Full experimental details will be published elsewhere. We wish to express our thanks to Prof. M. Ehrenstein, University of Pennsylvania, Philadelphia, for a generous gift of 6α- and 6β-hydroxy-Δ⁴-androstene-3.17-dione, and to Dr. A. Szpilfogel, N.V. Organon, Oss, for a sample of 6β-hydroxy-19-nortestosterone. We are also indebted to Dr. G. F. Marrian, Imperial Cancer Research Fund, London, and to Prof. M. Ehrenstein for reading the manuscript and for their helpful suggestions.

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Determination of Enzyme Activity by a Linear Measurement

The determination of the activity of proteolytic enzymes usually requires chemical analysis. A substrate, which can be either natural or synthetic, is being hydrolysed by the enzyme under specified conditions, and after a certain time the concentration of either the products or the remaining substrate is determined analytically. These methods are generally rather cumbersome. Furthermore, it is essential to perform the reaction under conditions such that only a small percentage of the substrate is transformed, so that the effect of the products on the reaction-rate should be negligible. This again leads to some analytical difficulties.

Let us suppose that a natural polymeric substance can be prepared in a homogeneous hydrated form, such as a gel, and then it can be cross-linked by some chemical means. A small number of cross-links, while leaving the chemical nature of the substrate virtually unchanged, will render the system insoluble, and relatively rigid. The matrix of the cross-linked substance may permit the penetration of small molecules or ions, but will be impenetrable to macromolecules, such as enzymes. Consequently, the action of the enzyme will be restricted entirely to the surface. Since the enzymatic breakdown products are usually soluble in aqueous media, these products will constantly be removed, and a fresh surface exposed to the enzyme.

If the enzyme-substrate interaction is restricted to the surface of the substrate, it is reasonable to assume that the reaction-rate will be proportional to the exposed surface area. Provided the substrate is homogeneous the reaction-rate will appear as a rate of change of volume of the substrate. These considerations can be expressed in the following relationship: $\frac{dV}{dt} = -kA$, where V is the volume of the substrate, t is the time, and A is the exposed surface area.

Denoting by dx the thickness of the layer of cross-linked substrate solubilized during time dt, then $dV = A\,dx$ or $\frac{dx}{dt} = -k$. In other words, the rate of change of any linear dimension perpendicular to the surface is constant. To determine k one measures a linear dimension perpendicular to the surface, for example, an edge of a cube, and plots the change of this length against time. A straight line should result, the slope of which is k. Since the concentration and the degree of cross-linking of the substrate are kept constant, different slopes will correspond to different enzyme activities. Measurement of the slope thus furnishes a means to determine enzyme activities.

The above principle has been applied successfully to the case of a number of proteolytic enzymes. A slightly modified gelatin was used as substrate, which is being manufactured by Schwarz BioResearch, Inc., under the trade name of 'Thiogel'. 'Thiogel' differs from ordinary gelatin in that it has a few homocysteine residues attached to the chain through peptide bonds with the lysine ε-amino groups. By virtue of this, 'Thiogel' has approximately 10 sulphydryl groups per 100,000 molecular weight. Oxidation of these sulphydryls to disulphide groups provides a convenient way to cross-link the polymer. 'Thiogel' gels can be cross-linked, for example, by atmospheric oxygen at slightly alkaline *p*H values.

The properties of cross-linked 'Thiogel' gels make them well suited for enzyme studies. These gels are rigid, unmeltable and can be cut into convenient geometric shapes. The chemical characteristics of gelatin are fully preserved. The equilibrium volume of the gel changes only very slightly with temperature, *p*H or ionic strength of the medium. For example, the linear expansion of the gel is only about 4 per cent when the temperature is raised from 4° C. to 40° C. The gel represents a protein in a highly hydrated form, and due to its high water content (94 per cent) it is freely permeable to small molecules and ions, such as the hydronium ion, yet completely impermeable to macromolecules, such as enzymes.

Cross-linked 'Thiogel' gel of about 6·5 per cent concentration has been prepared and cut into cubes of about 2 ml. volume. These cubes can be stored under water at room temperature, if some preservative, for example a few drops of chloroform, is added to the water. Before use a cube is immersed in about 200 ml. buffered solution and equilibrated for 20–30 min. at the temperature and *p*H of the determination. After this the distance between two parallel planes of the cube is measured with a micrometer. This initial

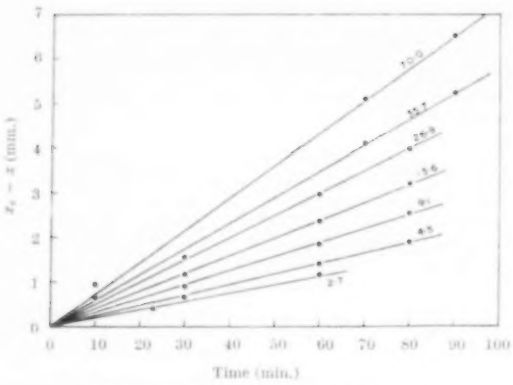

Fig. 1. Crystalline trypsin (*p*H 7·6, 30° C.)

distance was designated as x_0. At zero time a known amount of enzyme solution is added, and constant stirring applied. At regular intervals the cube is removed from the reaction mixture, rinsed with water to stop the reaction, and the distance x between the two parallel planes is again measured with the micrometer. After each measurement the cube is put back into the solution and the reaction continues. When plotting $x_0 - x$ against time, good linearity is generally obtained, so the slope can easily be determined and expressed in mm./hr. Sometimes at low enzyme concentrations a short induction period could be observed. In such cases it is advisable to determine x_0 about 10–20 min. after the addition of the enzyme.

Results obtained with crystalline trypsin are illustrated in Fig. 1. The trypsin concentrations (in mgm./l.) employed are given on the lines. All determinations were made at 36 ± 0·5° C. and at *p*H 7·6. The crystalline trypsin was prepared by Worthington Biochemical Corp., and its activity assayed about 8,500 units per mgm. determined with N-benzoyl arginine ethyl ester as substrate. Good linearity of $x_0 - x$ versus time was observed for at least 90 min. The slopes were reproducible to about 5 per cent. The magnitude of the slope is not proportional to the enzyme concentration, but follows the relationship: $\frac{x_0 - x}{t} = 0{\cdot}74\ c^{0{\cdot}437}$, where x is the distance in mm., t is the time in hours, and c is the trypsin concentration in mgm. per litre.

Other proteolytic enzymes are also being investigated using cross-linked 'Thiogel' as a substrate. Activated papain solubilizes the substrate readily. The change in linear dimension is proportional to time for about an hour. The slope is again proportional to a fractional power of the enzyme concentration. The action of crystalline pepsin and α-chymotrypsin was also studied, and it has been found that the rate of solubilization of cross-linked 'Thiogel' by these enzymes is lower by orders of magnitude as compared to the rate with trypsin. Thus the determination of the activity of trypsin can be performed in the presence of chymotrypsin.

The principal advantages of our method are that: (1) simple distance measurements are used instead of chemical analyses; (2) the enzyme–substrate interaction can be arrested merely by physical removal of the cross-linked gel from the solution; (3) the reaction can proceed over a long period of time without the reaction products having any effect on the rate since the region near the surface of the substrate may be continuously renewed. The sensitivity of our method depends on the precision of the distance measurement. The measurement need be made only over a short period of time if the substrate is a very thin sheet and one is observing the time of complete dissolution of the film. In Nature, proteases act on the surface of insoluble substrates and hence our system perhaps more closely resembles the natural condition than that with soluble protein substrates. When the cross-linked gel is removed from the enzyme solution, rinsed with water, and placed in a fresh buffer solution the dissolution of the substrate continues but at a progressively slower rate. In this manner the rate constant for the enzyme–substrate complex can be studied without the presence of free enzyme.

Our method should be applicable to other enzyme and substrate combinations. All that is required is that the enzyme be capable of cleaving either the polymer chain or the cross-linking bond of the hydrated cross-linked polymer substrate.

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Inhibition of Proteolytic Enzymes by Decarboxylated Amino-Acid Derivatives. Effect of Toluenesulphonyl(Tosyl)agmatine (4-Toluenesulphonamidobutylguanidine) on Thrombin and Trypsin

Proteolytic enzymes are known to catalyse the hydrolysis of specific amino-acid esters and amides[1]. Specificity is usually determined by the side-chain of the amino-acid contributing the carbonyl function to the bond being split, and, for several reasons, it may be inferred that this ester or amide bond lends very little to the initial binding of the substrate to the enzyme. Thus we suggest that derivatives of specific decarboxylated amino-acids would act as good competitive inhibitors of these enzymes. Since these derivatives would not be subjected to simultaneous hydrolysis, the effect would be longer lasting than that obtained with competing substrates.

One can readily construct a list of decarboxylated amino-acids which, when N-(amino) acylated, would be potential inhibitors for a number of enzymes. For example:

(1) Agmatine for thrombin, trypsin, plasmin and papain.

(2) 1,5-diaminopentane for trypsin and plasmin.

(3) 2-phenylethylamine or tyramine for chymotrypsin and pepsin.

(4) β-alanine or γ-aminobutyric acid for pepsin.

This list could, of course, be extended to include other enzymes with known specificities.

Thrombin (prepared by Rasmussen's method[2]) and trypsin (Worthington) were the enzymes chosen to test these ideas, and the kinetics of the hydrolysis of Nα-tosyl-L-arginine methyl ester (L-TAMe)[3] were studied with the use of a *p*H-stat (*p*H 7·7; μ, 0·069; 37°). Tosylagmatine (m.p. 178°) was synthesized and tested for inhibitory activity. The latter compound inhibited the ester hydrolysis by both enzymes in a competitive manner, with the results summarized in Table 1.

Table 1. TOSYLAGMATINE INHIBITION OF L-TAME HYDROLYSIS

Enzyme	Inverse Michaelis constant l./mole	K_I (inhibition constant) l./mole
Thrombin	$1{\cdot}79 \times 10^3$	$7{\cdot}6 \times 10$
Trypsin	$2{\cdot}78 \times 10^3$	$2{\cdot}9 \times 10^3$

The inhibitory effect of tosylagmatine on thrombin was also examined by the independent technique of measuring *p*-nitrophenol production from the substrate carbobenzoxyglycine *p*-nitrophenyl ester[4]. Tosylagmatine again proved to be a competitive inhibitor, $K_I = 8{\cdot}12 \times 10$ l./mole (at μ 0·133; *p*H 7·5; 38·4°). Furthermore, this compound effectively inhibited clotting in the thrombin-fibrinogen system, and it also greatly delayed the clotting time of whole plasma after recalcification.

One may conclude that, in spite of the fact that optical activity is lost by decarboxylation, derivatives of decarboxylated amino-acids retain most of the required characteristics of fit to the enzyme surface to classify them as competitive inhibitors. We have reasons for believing that modifications to the acylating group added to the decarboxylated amino-acids will yield even better inhibitors.

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PHYSIOLOGY

Effect of Iproniazid on the Antileukæmic Action of Reserpine

AN earlier communication reported the ability of reserpine to exert an antitumour effect[1]. This effect has been, in general, associated with the depressant action of the drug on the central nervous system[1–3]. Treatment with reserpine produced a significant increase in the survival-time of mice carrying advanced lymphoid leukæmia (*L*1210) and caused regression of the local tumour which develops at the inoculation site[1]. Robison *et al.* have made similar observations[2]. Belkin observed that reserpine and chlorpromazine inhibited the growth of the solid tumour, sarcoma 37[3]. Cranston[4], on the other hand, failed to demonstrate inhibitory action on recent transplants of spontaneous mammary adenocarcinoma in mice with reserpine, chlorpromazine, promazine or promethazine. Chorazy[5] found no inhibitory effect of chlorpromazine on Crocker sarcoma or Ehrlich carcinoma in mice.

Shore and Brodie[6] showed that, following pretreatment of rabbits with iproniazid (a monoamine oxidase inhibitor), reserpine administration resulted in excitatory and sympathomimetic responses. However, when iproniazid was administered after reserpine, it failed to alter the depressant effects on the central nervous system[6,7]. In an effort to dissociate the central depression induced by reserpine from its antitumour activity, experiments were conducted to determine the effect of prior administration of iproniazid on the antileukæmic effectiveness of reserpine in mice.

The reversal by iproniazid of the action of reserpine against advanced leukæmia is illustrated in Fig. 1. In this experiment daily injection of iproniazid (200 mgm./kgm.) was begun 6 days after the inoculation of mice with leukæmic cells. Reserpine was administered on day 8. The median survival-time of control leukæmic mice was eleven days. The median survival-time was increased progressively by increasing the dose of reserpine, reaching a maximum of 17 days at a dose of 12·5 mgm./kgm. of the drug. Daily injection of iproniazid reduced the median survival-time to that of the controls over the entire dose range of reserpine. Mice receiving iproniazid alone had the same median survival-time as the controls (11 days).

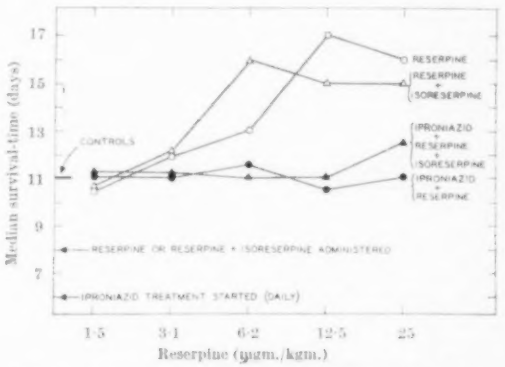

Fig. 1. The general methods have been previously described by Goldin *et al.* (refs. 9 and 10). Experiments were conducted in hybrid male mice (*BALB/c An* × *DBA/2J*)*F*$_1$, 8–10 weeks old and 20–25 gm. in body-weight. They were inoculated in the right hind leg with 0·1 ml. of a suspension of *L*1210 leukæmic cells. Treatment of advanced leukæmia was initiated when the local tumour reached a diameter of 9–12 mm., at which time the disease is systemic and can be transmitted by the blood. Iproniazid (200 mgm./kgm.) was administered intraperitoneally daily from day 6 until death. *Iso*reserpine (50 mgm./kgm.) was given subcutaneously on day 8. Reserpine at the doses noted was administered subcutaneously on day 8, 30 min. after the *iso*reserpine. Ten mice per group

The activity of 3-*iso*reserpine, a stereoisomer of reserpine, was of particular interest, since this compound is known to be devoid of depressant effects on the central nervous system. (One preparation of 3-*iso*reserpine produced marked central nervous system depression and antileukæmic activity similar to that seen with an effective dose of reserpine[1]. This preparation was later shown to be contaminated with 5 per cent reserpine.) The combination of 3-*iso*reserpine (50 mgm./kgm.) and reserpine (6·2 mgm./kgm.) prolonged survival-time three days over that observed with reserpine alone at this dose. This is suggestive of a potentiating effect by *iso*reserpine. This dose of *iso*reserpine alone did not produce depression of the central nervous system or increase the survival-time of mice with acute leukæmia. (This potentiating effect by 3-*iso*reserpine has been seen in several experiments. In addition, potentiation of reserpine action by 3-*iso*-reserpine was also demonstrated in the prolongation of pentobarbital-induced anæsthesia. In one experiment, reserpine alone (2·5 mgm./kgm.) prolonged

pentobarbital (70 mgm./kgm.) anæsthesia approximately four times, while in combination with 3-*iso*reserpine (50 mgm./kgm.), anæsthesia was extended six times[8]. Reserpine and 3-*iso*reserpine were injected subcutaneously four hours prior to intraperitoneal pentobarbital.) However, when the same dose of 3-*iso*reserpine (50 mgm./kgm.) was used in combination with larger doses of reserpine, no further enhancement of survival-time was obtained. Injection of iproniazid decreased the median survival-time to that of the controls up to a dose of 12·5 mgm./kgm. of reserpine with *iso*reserpine (50 mgm./kgm.). At the highest dose (25 mgm./kgm. reserpine with 50 mgm./kgm. *iso*reserpine), the median survival-time of 15 days was reduced by iproniazid to 12·5 days.

Iproniazid appeared to reverse the depressant action both of reserpine and of reserpine in combination with 3-*iso*reserpine. Iproniazid also prevented the loss of body-weight and inhibition of local tumour growth. Only in the group receiving 25 mgm./kgm. of reserpine and 50 mgm./kgm. of 3-*iso*reserpine with iproniazid was depression of the central nervous system evident. The reversal of reserpine action by iproniazid was also demonstrated in other experiments, including one in which the drugs were administered early (3 days after inoculation with leukæmic cells) in the course of the disease.

The experiments reported in this communication failed to demonstrate a dissociation of the depressant action of reserpine on the central nervous system from the ability of reserpine to inhibit leukæmic tumour growth. Therefore, it remains to be determined whether this correlation is indicative of a non-specific host-mediated antileukæmic effect or whether there is a specific antitumour action of reserpine.

We wish to thank Ciba Pharmaceutical Products, Inc., for the reserpine ('Serpasil') and 3-*iso*reserpine used in this study and Hoffmann-LaRoche, Inc., for the iproniazid ('Marsilid phosphate').

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Influence of Gamma-Aminobutyric Acid on the Acetylcholine Responses of the denervated Rat-Diaphragm Preparation

The literature on the actions of γ-aminobutyric acid was reviewed comprehensively by Elliott and Jasper in 1959[1]. Several investigators have demonstrated that it and related substances are normal products of brain metabolism, and that it has an important action on brain function as well as on certain peripheral nerve structures[2]. It is known to reverse the surface-negative post-synaptic potentials of the apical dendrites of the cerebral cortex[3] and also blocks transcallosal conduction when injected into the internal carotid artery[4]. The exact mechanisms by which these effects are produced are still unknown. Hence work on the influence of γ-aminobutyric acid on the acetylcholine responses of the denervated rat's diaphragm was undertaken.

Denervation was carried out on the right side by section of the roots of the phrenic nerve and the preparations were used at variable times after the denervation.

A triangular strip of the right half of the diaphragm was dissected carefully and fixed by means of threads to a special electrode holder made of 'Perspex'. The whole preparation was immersed in a bath containing Krebs–Henseleit solution[5] and oxygenated by passing very fine bubbles of 95 per cent oxygen and 5 per cent carbon dioxide. The temperature of the bath was maintained at 37° C. The muscle was connected by its tendinous portion to a lever, and the activity of the muscle was recorded on a slowly moving smoked drum.

The muscle could be stimulated either electrically using a physiological stimulator (Ritchie–Sneath) or chemically using acetylcholine. The complete details of the technique are published in my thesis on the denervated rat-diaphragm preparation published in 1951 (ref. 5).

Several experiments were conducted and the results were accepted only after each new finding could be repeated several times. The following results were obtained:

(1) 400–1,000 μgm. γ-aminobutyric acid had no action on the responses of the innervated rat's diaphragm, when stimulated by maximal stimuli through its nerve (rate 4–5/min.). This work confirms that of Hobbiger[2].

(2) 1,000 μgm. of the drug has no action on the responses of the denervated rat-diaphragm prepara-

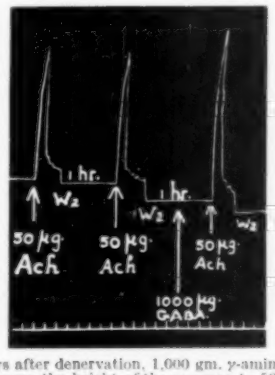

Fig. 1. 7 days after denervation. 1,000 gm. γ-aminobutyric acid not only increases the height of the response to 50 μgm. acetylcholine but also brings about a better relaxation of the muscle

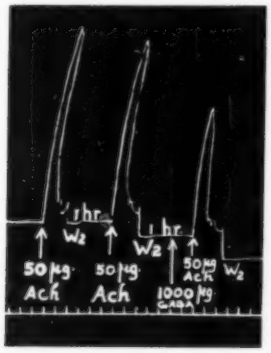

Fig. 2. 8 days after denervation, 1,000 gm. γ-aminobutyric acid not only reduces the height of the response to 50 µgm. acetylcholine but also brings about better relaxation of the muscle

tion (8–10 days after denervation) when stimulated by maximal stimuli at a rate of 4–5 per min.

(3) In my thesis on the denervated rat diaphragm preparation[5], I observed that the first noticeable response to a test dose of acetylcholine (50 µgm.) was obtained on the third or fourth day after nerve section. The sensitivity thereafter increased progressively and was fairly well established by the second week. This state was maintained up to the fifth to sixth week, and then there was a steady decline to almost nothing by the third month after denervation.

As the sensitivity of the denervated preparation alters with time, the influence of γ-aminobutyric acid on the acetylcholine responses was studied with preparations 7, 8, 9 and 10 days after denervation. It was noticed that 1,000 µgm. produced two main changes to the responses of the denervated preparation to 50 µgm. of acetylcholine: (*a*) An alteration in the height of the contracture. The height was always increased in 7-day preparations and diminished in 8-day preparations (Figs. 1 and 2). (*b*) A more complete relaxation of the muscle was noticed in both preparations. It was also found that 1,000 µgm. γ-aminobutyric acid had variable actions on the acetylcholine responses of 9-day-old preparations and no influence whatsoever on 10-day-old preparations.

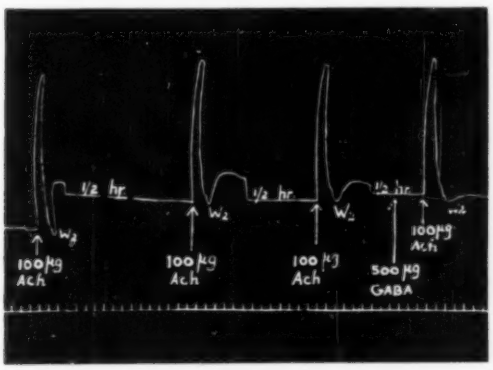

Fig. 3. Responses of a denervated preparation (8 days) when immersed in Krebs–Henseleit solution containing one quarter the normal concentration of potassium chloride. 500 µgm. γ-aminobutyric acid is found to bring about a better relaxation of the muscle after the same dose of acetylcholine (100 µgm.)

(4) It was noticed that 500 µgm. γ-aminobutyric acid abolished the second contracture that occurs when 100 µgm. of acetylcholine was introduced into a bath containing a denervated preparation with a potassium concentration one quarter that found in normal Krebs solution (normal Krebs has 5·52 gm. potassium chloride/15 litres, Fig. 3).

(5) 1,000 µgm. γ-aminobutyric acid had no influence on the contracture produced by 50 µgm. adrenaline on the denervated rat-diaphragm preparation.

This work has been done in the Department of Physiology, University of Ceylon, since 1958.

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Effect of Duodenal Administration of Highly Unsaturated Fatty Acids on Composition of Ruminant Depot Fat

Although linolenic acid is the main fatty acid of pasture lipids, the fats of pasture-fed ruminants contain little if any of this constituent[1]. Also, feeding large quantities of highly unsaturated oils to ruminants has had no perceptible effect on the unsaturation of their depot fats[2]. Various workers[3–5] have shown that micro-organisms in the rumen hydrogenate dietary unsaturated fatty acids, and this has been presumed to explain the low content of highly unsaturated fatty acids in the depot fats of ruminants.

To test whether this explanation was correct the rumen micro-organisms have been by-passed and dietary lipids rich in linoleic and linolenic acids presented to the tissues by administering linseed oil through a duodenal cannula to a sheep, and the effect on the composition of the depot fat observed.

A mature Merino ewe was cannulated about 6 in. from the pylorus and fed on chaffed lucerne hay. About 40 ml. of an emulsion of 8 vol. of linseed oil and 1 vol. of bile were given each day, half in the morning and half in the evening, for six weeks. The perinephric fat was then obtained after killing and the fatty acids subjected to gas-liquid chromatography. Results are given in Table 1.

Palmitic, stearic and C_{18} monoene (oleic) contents of the fat were within the normal range, but the C_{18} diene (linoleic acid) and triene (linolenic acid) contents were greatly above the normal range of 1–2 per cent. This shows that the main fatty acid constituents—linoleic and linolenic acids—of linseed oil

Table 1. Fatty Acid Composition of Perinephric Fat (molar per cent)

	n-Saturated	Branched saturated	Unsaturated
C_{16}	0·20	—	—
C_{18}	trace	—	—
C_{14}	1·20	0·10	—
C_{15}	1·00	0·89	—
C_{16}	26·83	—	1·09
C_{17}	2·99	2·19	—
C_{18}	27·12	—	Monoene 18·55 Diene 7·87 Triene 9·97

are capable of being deposited in the depot fats of ruminants as in the case of non-ruminants provided they are not first subjected to the action of the rumen micro-organisms.

Thus the hypothesis mentioned here, that the differences between the depot fats of ruminants and non-ruminants arise from the hydrogenation of the unsaturated dietary fats in the rumen, receives further support.

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Photomotor Reflex as an Indicator of Consciousness during Curarization

WHEN a relaxant is used in conjunction with a general anæsthetic, a new problem arises in assessment of the depth of anæsthesia: the reflexes which normally indicate returning consciousness and awareness of pain cannot appear if the patient is under the influence of a relaxant. Thus, if only reflexes involving voluntary muscle are used, it is possible, in the presence of a relaxant, for anæsthesia to lighten so that surgery is performed on a conscious paralysed patient without surgeon or anæsthetist being aware of the situation. This has been recorded more than once in human medicine, the patient having described the situation after the operation[1]. The same situation can occur in operations on animals when an anæsthetic is used in conjunction with a relaxant; but in this case the patient cannot afterwards direct attention to the mistake. Such circumstances produce problems with humanitarian and legal aspects for the veterinarian, as Finn[2] has pointed out; they also complicate the interpretation of the pain clause for research workers holding a vivisection licence.

The electroencephalograph can be used to assess depth of anæsthesia in a curarized man or animal, but it is not always available, and needs some skill in interpretation. Experiments have therefore been carried out to discover a simple method of assessing depth of consciousness in curarized dogs, the electroencephalograph being used as a criterion of the activity of the brain. Pentobarbitone sodium, thiopentone sodium and ether were used as anæsthetics, and succinylcholine chloride as the relaxant.

It was found that the photomotor reflex (change in size of pupil of eye with sudden change in light intensity), unlike the other reflexes commonly used for testing anæsthesia, gave a reliable indication of returning consciousness in the presence of a relaxant. It became positive as the dog passed from stage III (surgical anæsthesia) to stage II (excitement). Pre-medication with atropine did not invalidate the reflex, provided that the dose of atropine did not exceed 0·032 mgm./kgm. body-weight. It seems likely that this reflex would also be useful in human patients in similar circumstances. The work will be described in more detail elsewhere.

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Spiral Nerve-endings (Proprioceptors) in the Human Vocal Muscle

THE problem of the proprioceptive innervation of the human vocal muscle is still controversial[1]. The presence of a proprioceptive mechanism controlling the fine adjustments of the vocal cords has been postulated by some authors; it has been rejected on theoretical grounds by others. Paulsen[2] assumes that the tension of the vocal muscle would have central control alone. A peripheral proprioceptive mechanism would be rather a hindrance for normal phonation. The same was said to be true of the extrinsic eye muscles, in which nevertheless proprioceptors have been demonstrated within the past ten years histologically as well as by electrical records[3–5].

To clear up the question, we have cut the vocal muscle of men who had shown no evidence of neurological disease during life, in longitudinal frozen sections of 40–60μ thickness. With a modification of the silver staining Bielschowsky–Gros method, we succeeded in showing spiral nerve endings in this muscle, which may be interpreted as mechanoreceptors responding to stretch or shortening of the fibres (Fig. 1).

These spiral structures have been found to form a group of 3–5 nerve endings occupying a small place within the motor innervation zone[6] near the free inner board of the muscle at the level of the vocal

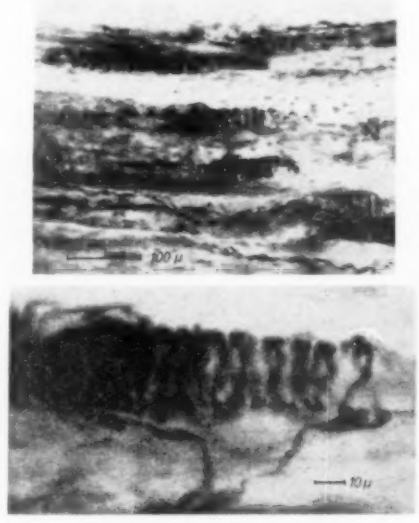

Fig. 1. Spiral nerve-endings in the human vocal muscle; silver staining. Top: Group of receptors in the small diameter muscle fibre area (inner board) of the muscle. Bottom: One receptor with higher magnitude; double spiral turns in the left part around two small muscle fibres

string. They look like the annulo-spiral endings in the equatorial region of muscle spindles. Their length varies from 100 to 200μ. The nerve fibre is coiled up around one or two small muscle fibres in steep turns. Between the spiral endings are closely packed nuclei, suggesting a region of intense metabolic activity. The size of muscle fibre varies in the vocal muscle from 10 to 60μ. The spiral nerve-endings and their associated muscle fibres lie within a region where the diameter of most of the muscle fibres does not exceed 10μ. One or two end-plates of the associated fibres which stained in some cases were found within 100μ from the spiral district. There is no histological evidence that an efferent gamma-system exists in the vocal proprioceptive mechanism. A connective tissue wrap around the spindle organ does not seem to be present.

These structures differ from the classical form of spindles described by Kühne and Ruffini. There is perhaps some relation to the spiral nerve-endings in extrinsic eye muscles of which the receptor properties have been shown[4]. The spiral ending in the vocal muscle may be a rather primitive form of proprioceptor, which is no surprise in a muscle of such particular origin (Goerttler).

The fact that these spiral nerve-endings are not encapsulated and the inner muscle fibre diameter does not differ markedly from the diameter of the surrounding muscle fibres may be the reason why they have been overlooked in transverse sections. They could relate to the recently described myotatic reflex elicited in the human vocal cord[7].

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Active Transport of Foreign Pyrimidines across the Intestinal Epithelium

The small intestine of mammals possesses at least three independent active transport processes for the absorption of organic compounds: one for monosaccharides like glucose and galactose[1]; one for L-amino-acids[2]; and one for pyrimidines like uracil and thymine[3]. These specialized absorption processes have a number of characteristics in common which distinguish them from the process of simple diffusion: the substrate is transferred against a concentration gradient; the transport systems become saturated at high concentrations of substrate; and one substrate depresses the passage of another by competing with it for the transport process.

In contrast to the natural cell substrates, most drugs and other foreign organic compounds are absorbed mainly by simple diffusion[4,5]. The intestinal epithelium behaves towards these substances as an inert, lipid-like layer, readily penetrated by lipid-soluble, undissociated molecules, and penetrated with difficulty by lipid-insoluble molecules and ions.

The present work indicates that foreign organic compounds similar in structure to a normal substrate can be absorbed by a specialized transport process. Evidence is presented that two foreign pyrimidines with anti-tumour activity, 5-fluorouracil and 5-bromouracil, are actively transported by the pyrimidine transport system of the intestine.

For the experiments, male Sprague-Dawley rats (120–130 gm.), fasted for 20 hr. but allowed free access to water, were killed by decapitation, and the upper part of the small intestine was removed. Sacs of everted intestine[6], 20 cm. long, were filled with 2 ml. of bicarbonate-saline solution[7] which contained 1 gm. of glucose per litre and various concentrations of uracil-2-^{14}C, 5-fluorouracil-2-^{14}C, or 5-bromouracil-2-^{14}C. The sacs were suspended in 15 ml. of the same fluid contained in 50-ml. beakers, and the beakers shaken in a Dubnoff metabolic shaker (90 oscillations per min.) at 37° C. in an atmosphere of 95 per cent oxygen and 5 per cent carbon dioxide. After 1 hr., the mucosal and serosal solutions were collected, and the concentration of pyrimidine estimated from the radioactivity of the solutions.

Evidence that the labelled compounds are not altered metabolically by the intestine was provided by paper chromatography of the pyrimidine solutions incubated with the intestine. Chromatograms developed in either *n*-butanol/acetic acid/water (20 : 6 : 17 v/v/v) or ethyl acetate saturated with 0·1 *M* acetate buffer (*p*H 5·3) revealed single radioactive spots with R_F values the same as those of the non-incubated pyrimidines chromatographed on the same sheets.

The extent of transfer of the pyrimidines across the intestinal epithelium, against a concentration gradient, is shown in Table 1. When the initial concentration of pyrimidine was 0·02 m.mol./litre, fluorouracil was transported to about the same extent as uracil, attaining a serosal/mucosal concentration ratio of 4·5; bromouracil was transported to a somewhat smaller degree, attaining a serosal/mucosal ratio of 3.

Table 1. Intestinal Transfer of Pyrimidines against a Concentration Gradient *in vitro*

Pyrimidine	Concentration of pyrimidine (m.mol./l.)			Final, serosal to mucosal concentration ratio
	Initial, mucosal and serosal solutions	Final, mucosal solution	Final, serosal solution	
Uracil	0·020	0·012	0·056	4·7 ± 0·3*
5-Fluorouracil	0·020	0·011	0·049	4·5 ± 0·3†
5-Bromouracil	0·020	0·013	0·039	3·0 ± 0·2†

* Mean value for 27 animals ± *S.E.*
† Mean value for 8 animals ± *S.E.*

The transport process became saturated at high concentrations of the pyrimidines. For example, on raising the concentration of fluorouracil or bromouracil to 0·5 m.mol./litre, the serosal/mucosal concentration ratios declined to values approaching unity.

An indication that fluorouracil, bromouracil and uracil cross the intestinal epithelium by the same transport system was obtained from experiments in which the foreign pyrimidines depressed the transfer of uracil. For example, at a concentration of 5 m.mol./litre, fluorouracil and bromouracil inhibited completely the active transport of 0·02 millimolar uracil.

The nature of the substituent at the 5-position of the uracil molecule does not appear to be of great

importance in determining the extent to which the molecule is actively transported, since uracil, 5-methyluracil (thymine), 5-fluorouracil and 5-bromouracil are all transported across the intestinal epithelium to a similar extent. On the other hand, since the hydrogen, fluorine and bromine atoms and the methyl group have Van der Waals radii of a similar magnitude (1·2–2·0 A.)[6], it is possible that a considerably larger substituent would interfere with transport of the molecule. Investigations are now being made to determine the structural characteristics of pyrimidines which are required for active transport.

The results of this work suggest that anti-metabolites may not only compete with normal substrates for metabolic processes within the cell, but may also compete with these substrates for transport into the cell.

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Changes of Quantity of Flavin in the Brain after Peripheral Administration of Flavins

It has been reported from our laboratory[1] that flavins produce a change in the electroencephalogram, and that the effect produced by chlorpromazine is partly reversed by flavin adenine dinucleotide. These results suggest that the flavins act on the brain *in situ*. In an attempt to discover the mechanism of action of flavins, their penetration of the blood–brain barrier was examined by determining the amount of flavin in the rat brain after peripheral injection of flavins.

Flavin adenine dinucleotide was prepared by the method of Yagi *et al.*[2]. Flavin mononucleotide and riboflavin were purified chromatographically from commercial samples. Albino rats weighing about 100 gm. were used for the experiment. Fifty animals, 10 days after feeding under the same conditions, were divided into five groups, each group consisting of 10 animals. The animals of the first group were used as control, and injected with water intra-abdominally. Each animal of three groups was injected intra-abdominally with 20 mgm./kgm. (calculated as riboflavin) of flavin adenine dinucleotide, flavin mononucleotide, or riboflavin aqueous solution respectively. The animals of the fifth group were injected with 50 mgm./kgm. of an aqueous solution of riboflavin. One hour after the injection, a blood sample was collected from the carotid artery, and then the animal was killed by decapitation. The quantity of flavin in the brain was measured by the lumiflavin fluorescence method described by Yagi[3], and that in the blood sample was measured by the micro-method for riboflavin in blood described by Yagi *et al.*[4].

Table 1. Quantity of Flavin (calculated as Riboflavin) in Rat Brain after the Injection of Flavins (μgm./gm. of Wet Tissue)

	Means of population ($n = 10$), ($\alpha = 0{\cdot}01$)
Controls	3·32 ± 0·35
After the injection of:	
Flavin adenine dinucleotide (20 mgm./kgm.)	3·75 ± 0·69
Flavin mononucleotide (20 mgm./kgm.)	3·73 ± 0·85
Riboflavin (20 mgm./kgm.)	5·18 ± 0·74
Riboflavin (50 mgm./kgm.)	7·37 ± 0·87

The quantities of flavin in the brain after the injection of flavins are shown in Table 1. The variances in the normal cases were rather small, and the values were in good agreement with the earlier results[5]. After the injection of flavin adenine dinucleotide, the increase of flavin in the brain was significant by the *t*-test with $\alpha = 0{\cdot}1$. In the case of flavin mononucleotide, the increase was significant with $\alpha = 0{\cdot}2$. However, after the administration of 20 mgm./kgm. of riboflavin, flavin in the brain increased, the difference being significant even with $\alpha = 0{\cdot}01$. After the injection of 50 mgm./kgm. of riboflavin, further increase of flavin was observed.

The increases of flavins in blood at 1 hr. after the administration to each animal of 20 mgm./kgm. of flavin were almost equal for the three types of flavins, being less than 1 μgm./ml. of blood. Since the brain contains 0·024 ml. of blood per gm. on the average[6], the increase of flavins due to the blood content of the tissue was about 0·02 μgm./gm. The corrected amounts found by subtracting the values due to the blood from that of the tissue gave a similar result.

It seems, therefore, that the increase of flavin in the brain was due to the penetration of injected flavins from the blood into the brain tissue. It is considered that the flavins penetrate the blood–brain barrier, and that riboflavin can cross this barrier more easily than flavin mononucleotide or flavin adenine dinucleotide.

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Reversible Block of Axonal Conduction by Curare after Treatment with Cobra Venom and a Detergent

The recent experiments of Abbott, Hill and Howarth[1] have revealed that the remarkably high initial heat produced in nerve fibres coincides roughly with electrical activity. This finding re-emphasizes the necessity of explaining electrical activity on a chemical basis. Nachmansohn's theory[2] attributes the change of conductance which initiates the ion movements to the reaction of acetylcholine with a receptor protein. One of the main objections to this theory is the lack of effect of acetylcholine and curare on axons in contrast to their powerful action at junctions. This failure was attributed to the existence of structural barriers for lipid-insoluble quaternary ammonium

compounds. Evidence supporting this contention was obtained in experiments on squid giant axons: acetylcholine, labelled with nitrogen-15, and prostigmine failed to penetrate into the axoplasm whereas lipid-soluble tertiary compounds did so readily[2,3]. However, at the nodes of Ranvier, where these barriers are relatively small, curare can rapidly and reversibly block conduction, as shown in recent work by Dettbarn[5]. Walsh and Deal[6] succeeded in partially breaking down these barriers in frog sciatic nerve by treatment with the cationic detergent cetyltrimethylammonium bromide, after which curare and other quaternary ammonium compounds, ordinarily inert on the intact axon, caused reversible block of conduction.

In the present work the squid giant axon was pre-treated with a variety of enzymes and detergents in an attempt to permit the action of curare and other compounds. Of the many pre-treatments used, the combination of *Naja naja* cobra venom (10 μgm./ml.) and cetyltrimethylammonium chloride (20 μgm./ml.) applied for 30 min. was most effective in permitting the action of curare applied afterwards on electrical activity. In many experiments, complete and reversible block of conduction was obtained (Fig. 1), sometimes at a curare concentration as low as 5×10^{-4} *M*; $1{\cdot}4 \times 10^{-3}$ *M* curare (10 mgm./ml.) on the intact nerve produced little if any effect.

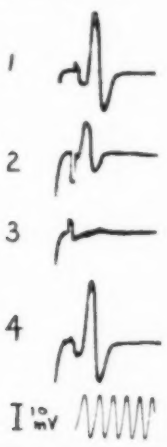

Fig. 1. Effect of curare on squid axon following pre-treatment with 10 μgm./ml. cobra venom plus 20 μgm./ml. cetyltrimethylammonium chloride. (1) Control after 30 min. pre-treatment with cobra venum plus cetyltrimethylammonium chloride. Pre-treatment had no effect on spike height. (2) and (3), 5 and 10 min. after application of $1{\cdot}4 \times 10^{-3}$ *M* curare. Conduction was completely blocked, as shown in 3, despite greatly increased stimulus strength. (4) 10 min. after return to sea water. Time signal: 850 c./sec.

The action of a series of tertiary compounds including local anæsthetics (procaine and dibucaine) on the untreated axon was also studied. In each case, these compounds affected conduction at concentrations similar to those required to block synaptic junctions of a single isolated electroplax preparation[7]. Local anæsthetics such as tetracaine and dibucaine, known to block all axonal activity, have recently been shown to react in a highly specific way with the acetylcholine receptor protein[8]. Curare has a high affinity to this protein[9] and has now been shown to block axonal conduction. These results suggest that the receptor protein is present in the axon and is essential for electrical activity. Failure of lipid-insoluble cationic substances such as curare to act on the intact nerve is evidently due to the protection of such receptors by permeability barriers and not to a mechanism which differs basically from that at the junction. Cobra venom and cetyltrimethylammonium chloride probably break down these barriers to an extent which permits curare to react with the receptors and block conduction. The evidence for the action of curare on axonal conduction, to be published in greater detail elsewhere, together with the other results mentioned above, provide new support for Nachmansohn's theory.

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HÆMATOLOGY

Hæmoglobin Variants in Sarawak and North Borneo

ABNORMAL hæmoglobins are frequent in south-east Asia[1]. However, only one report of a search for abnormal hæmoglobin variants in Sarawak has so far appeared: among 101 blood samples from Land Dyaks and 85 from Sea Dyaks, only one (from a Land Dyak) contained an abnormal variant and represented the heterozygous state for hæmoglobin *E*[2].

Recently, 1,355 blood samples from Sarawak were studied by the technique of filter-paper electrophoresis at *p*H 8·6. The distribution of samples was Sea Dyaks 68, Land Dyaks 341, Chinese 742, Malay 166, Indian 13, European 23, Eurasian 1 and Filipino 1. All the samples were taken from persons in the First Division of Sarawak and largely from areas within reach of Kuching, and came from hospital in-patients, ante-natal cases and a few out-patients and candidates for government posts. The age distribution was 3–72 years and the sexes were approximately equally represented. All the samples from Sea Dyaks, Land Dyaks, Indians and the Eurasian and Filipino were found to contain only normal adult hæmoglobin (hæmoglobin *A*). Among the samples from Chinese, Malay and European subjects, respectively, 2, 5 and 1 contained a mixture of hæmoglobins *A* and *E*, while 2 samples from Chinese contained a mixture of hæmoglobins *A* and a 'slow' hæmoglobin with properties very similar to those of hæmoglobin *Q*. It has not proved possible to characterize this slow hæmoglobin in great detail. The sample containing hæmoglobins *A* and *E* from

a European 'white' came from an English woman whose lineage it was not possible to trace.

Through the courtesy of Prof. T. A. Lloyd Davies, of the Department of Social Medicine and Public Health, University of Malaya in Singapore, it was possible to study 53 blood samples obtained from Muruts inhabiting the Crown Colony of North Borneo. The Muruts are "small, stocky, mongoloid people, with light brown skin and straight black hair"[1]. They are a group of related pagan tribes which have been relatively isolated because they were practising head-hunters until recently. All but 3 of these samples contained only haemoglobin *A*; in the rest the pattern was that of a mixture of haemoglobins *A* and *E*. The slow component in these three samples was probably not haemoglobin A_2, since it comprised more than 20 per cent of the total haemoglobin[4].

The absence of any abnormal variants among the Dyaks examined and the solitary finding of one example of haemoglobin *E* trait by Colbourne *et al.*[2] indicates the infrequency of abnormal variants in these people. The finding of haemoglobin *E* in 2 Chinese and in 5 Malays parallels similar findings among these ethnic groups in Singapore and Malaya[3]. The existence of a focus of a haemoglobin, which is probably *Q*, among the Chinese in Kuching is indicated.

We are grateful to Dr. W. Glyn Evans, director of Medical Services, Sarawak, for permission to carry out this investigation.

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Production of *B* Character on Human Erythrocytes by Hæmosensitization with Purified *Escherichia coli O* 86 Substance

The serological specificity of the human blood group substances *A* and *B* is due to characteristic polysaccharide components[1]. Recently, the same has been found to apply to the *Salmonella O* antigen[2]. The serologically active component, a lipopolysaccharide, was isolated from the bacteria and submitted to chemical analysis, which showed that in various strains within the same *O* group or *O* sub-group, the *O* antigen is of an identical qualitative-chemical composition, that is, it contains the same 'Zuckerbaustoine'.

A lipopolysaccharide from *E. coli O* 86, obtained by this procedure, was placed at my disposal. An investigation was conducted to ascertain whether this purified preparation, of known qualitative-chemical composition, might possess blood-group activity of *A* and/or *B* specificity. By previous work[3,4] and my earlier work it had been shown that *E. coli O* 86 contained *A*-like and *B*-like substances. The investigation was carried out by hæmosensitizing human *O* cells with the purified lipopolysaccharide by the following procedure:

10 mgm. of lipopolysaccharide from *E. coli O* 86 was dissolved during heating in 10 ml. re-distilled, sterile 0·9 per cent saline solution (stock solution). For purposes of the hæmosensitization the stock solution was diluted 10 times with sterile 0·9 per cent saline solution. To 20 volumes of this solution was added 1 volume of packed, thoroughly washed *O* cells, and the mixture was incubated in a water-bath at 37° C. for 1 hr. After incubation, the blood cells were again washed and then tested in various blood-group reagents of anti-*A* and anti-*B* specificities. The results are given in Table 1.

Table 1. Sensitized *O* cells and Normal *B* cells in different anti-*B* reagents

(All reactions performed on a glass plate at 20° C.; readings after 10 min.)

	Human *AB* serum or anti-*A*	Human anti-*B*	Human anti-*B* absorbed with human *B*	Human anti-*B* absorbed with rabbit *B* (β_1)	Human anti-*B* absorbed with sensitized *O*
Normal *O* cells	–	–	–	–	–
Sensitized *O* cells	–	+ + +	+	+	–
Normal *B* cells	–	+ + +	–	–	+ +

	Rabbit immune anti-*B* (β_1)	Chicken immune anti-*B* (β_2)	Chicken immune anti-*B* absorbed with human *B*	Chicken immune anti-*B* absorbed with rabbit *B*	Chicken immune anti-*B* absorbed with sensitized *O*
Normal *O* cells	–	–	–	–	–
Sensitized *O* cells	+ +	+ +	–	–	–
Normal *B* cells	+ + +	+ + +	–	–	+ +

	Eluate from human *B* cells incubated with human anti-*B*	Eluate from sensitized *O* cells incubated with human anti-*B*	Eluate from sensitized *O* cells incubated with human anti-*B* and absorbed with human *B*	Eluate from sensitized *O* cells incubated with human anti-*B* and absorbed with rabbit *B*
Normal *O* cells	–	–	–	–
Sensitized *O* cells	–	+ +	–	–
Normal *B* cells	+ + +	+ + +	–	–

The sensitized *O* cells agglutinated in human anti-*B* sera, showing a strength of agglutination apparently dependent on the strength of the anti-*B* present. In undiluted serum the strength of agglutination was equal to or slightly weaker than that with normal *B* cells, but the titre against sensitized *O* cells was lower than against normal *B* cells. The agglutination was weakened or abolished by addition of *B* saliva, but not of *A* saliva or *O* saliva, by absorption with *B* cells, but not with *A* cells or *O* cells. In human anti-*A* sera or *AB* sera, there was generally a weak reaction of the same order of magnitude as the reaction which remained in the neutralized or absorbed anti-*B* sera.

Incubation of the sensitized *O* cells in human anti-*B* sera with elution afterwards of the antibody (by the Landsteiner method) resulted in an eluate reacting with *B* cells and sensitized *O* cells, but not with *A* cells or with normal *O* cells. On the other hand, an eluate made by using the same serum and *B* cells reacted exclusively with *B* cells, not with sensitized *O* cells.

Absorption of human anti-*B* sera with sensitized *O* cells induced an unmistakable reduction of the anti-*B* content. In the same way, the lipopolysaccharide solution was able to abolish the reaction of *B* cells in anti-*B* sera. Conversely, there was no neutralizing effect of the solution on the agglutination of *A* cells in anti-*A* sera.

Sensitized *O* cells were tested in rabbit immune anti-*B* (specificity β_1) and chicken immune anti-*B* (specificity β_2)[5]. The cells gave a negative reaction with rabbit immune anti-*B*, but a positive reaction with chicken immune anti-*B*. Absorption of chicken immune anti-*B* with rabbit cells abolished the reaction with sensitized *O* cells.

As mentioned previously, the sensitized *O* cells reacted with practically all the human anti-*A* sera and *AB* sera tested. There was no distinct difference between anti-*A* sera and *AB* sera. The sensitized blood cells gave negative reaction with anti-*T*. Thus, the purified lipopolysaccharide from *E. coli O* 86 must contain a reactive group against which most human beings possess an antibody.

Analysis of the preliminary results, as shown in the table, supports the presumption that the purified lipopolysaccharide from *E. coli O* 86 contains a reactive group similar to blood-group factor *B* in man and the *B*-like factor in rabbit cells. However, it does not seem to be identical with human *B* or rabbit *B*.

The so-called A^b cells[6-9] also had an atypical *B* character which was weaker than the normal *B* factor on human *B* cells. It might be imagined, therefore, that they bear a certain relation to the artificial *B* cells produced in this work. It has, in fact, been suggested that the A^b character might be considered to be acquired[7-9]. There are points of resemblance between the *B* character on the A^b cells and the *B* character on the sensitized blood cells, but there are differences as well. While the A^b character has been found only in *A* persons, there was no demonstrable difference, qualitative or quantitative, between sensitized *A* cells and sensitized *O* cells, when tested in a series of anti-*B* sera and *AB* sera. Further work is needed, however, to elucidate the relation between the *B* characters on the different types of blood cells.

I am indebted to Dr. O. Westphal, A. Wander Forschungsinstitut, Freiburg-Zähringen, for the generous supply of purified lipopolysaccharide from *E. coli O* 86, and I wish to thank Dr. F. Kauffmann and Dr. F. Orskov, of the International Salmonella and Escherichia Centre, Statens Seruminstitut, Copenhagen, for valuable assistance.

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PATHOLOGY

Effect of Essential Oils on Atherosclerosis of Cholesterol-fed Rabbits

On glancing through the international literature we do not find any information on the therapeutical application of well-known pharmacological products, like the essential oils, in the treatment of atherosclerosis, and no experiments have been carried out on this subject. The essential oils are ingredients of plants and are readily soluble in most of the organic solvents. They contain mainly various terpenes like menthol, camphor, pinene, borneol, cineol and other compounds. The chemical structure of the majority of terpenes has been determined.

The terpenes preferably penetrate into cells of high lipoid content. Menthol presents an affinity to nerve receptors, camphor—according to several authors—to the vasomotor centre. Alpha-pinene, like the bicyclic terpenes, exerts a chemotactic effect on leucocytes[1-4].

The physico-chemical properties of essential oils and their remarkable affinity to cells with high lipoid content induced us to test their efficacy in atherosclerosis. In our investigations we used a terpene mixture consisting of borneol, camphenes, cineol, menthol, menthone and pinene. (We owe thanks to Messrs. Rowa-Wagner G.m.b.H., Bensberg/Cologne, Western Germany, for providing us with the necessary quantities of this product.)

Our investigations were carried out on male rabbits weighing 3,000 gm. We induced atherosclerosis by cholesterol feeding as described by Anichkov and Chalatov[5]. 1 gm. of cholesterol added to bran-balls was given daily to 20 rabbits of the first test group and to 12 rabbits of the second. Basically, we applied 1 ml. of the terpene mixture by subcutaneous injection every other day to ten rabbits of the first test group. Due to the occurrence of sterile abscesses in some rabbits 6 wk. later, the administration of the terpene mixture was continued orally for another 6 wk. Six animals of the second test group received the remedy orally throughout the whole test period of 3 months. Rabbit food consisted of lucerne and beet besides the bran-balls.

In both test groups four animals died. Thus 12 animals of each group remained for evaluation. Blood cholesterol-level was determined at the beginning, and at the end of our investigations showed an increase up to 1,048 ± 82 mgm. per cent, in comparison with an initial average level of 130 ± 24 mgm. per cent. We encountered a similar rise of cholesterol esters, the rate of which, however, was somewhat less than that of total cholesterol. Paper electrophoresis revealed a very significant increase of the beta-lipoprotein fraction in both groups. In autopsy we established hepatomegaly; a considerable storage of cholesterol in the liver was found in the animals of both groups by histochemical methods. Examination of the aortal intima revealed decisive differences between the terpene-treated animals and the controls. In the controls of the first series, we observed widespread atherosclerotic plaques in the aortal intima amounting to more than 45 per cent of total aortal surface as measured by planimeter. The number as well as the extension of these plaques in the aortæ of the treated animals of the same group were much less than in the controls; they affected merely 13 per cent of the total aortal intima (Fig. 1). In the other test group, however, essentially no atherosclerotic

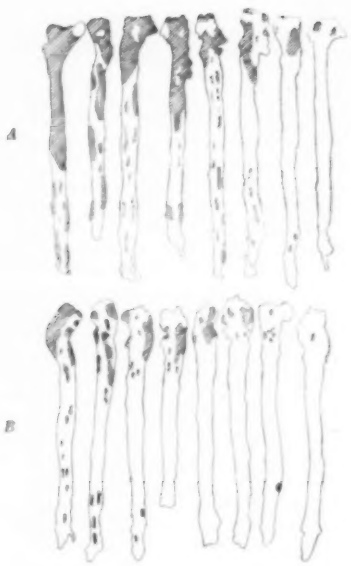

Fig. 1. *A*, Aortæ of terpene-treated animals; *B*, aortæ of controls

plaques appeared in the aortæ of the treated animals compared with those of the untreated ones (Fig. 2).

These findings are rather noteworthy in view of the fact that terpene treatment did not impair the absorption or storage of cholesterol, and that it did not inhibit the increase of serum cholesterol-level. Nevertheless, the terpene compound prevented remarkably the development of atherosclerotic plaques.

Fig. 2. *A*, Aortæ of terpene-treated animals; *B*, aortæ of controls

Impaired lipoid metabolism is nowadays generally considered to be one of the most important pathogenic factors causing atherosclerosis[6-9]. All the therapeutical measures have in common the tendency to remove these disorders. In dietetics, the important role of unsaturated fatty acids has been pointed out recently[10]. All the procedures aim at normalizing the blood lipoid-level. It is well known, however, that a high level of serum cholesterol is not always associated with atherosclerosis, as demonstrated by cortisone-induced hypercholesterolæmia, by nephrosis, and by certain forms of cirrhosis. Gerő and co-workers[11] reported a significant decrease of atherosclerosis originating from lipoprotein immunization in spite of high cholesterol-levels. We also suggest that the formation of atherosclerotic plaques is prevented by a terpene treatment, notwithstanding the high levels of serum cholesterol. We suppose that this effect of the terpenes partly results either from some competitive inhibition, or perhaps they act by blocking mediatory factors promoting the penetration of lipoids into the arterial wall.

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Influence of Uræmia on the Survival of Skin Homografts

Couch *et al.*[1] have shown that homografts of skin may survive for prolonged periods in a uræmic patient. They considered that this extended survival might be due to an impairment of immune responses in the patient. However, there is evidence to show that in patients with both acute and chronic uræmia the production of certain classical antibodies is within normal limits[1-4]. Stoloff *et al.*[3] have suggested that while the synthesis of classical antibodies may be impaired by uræmia, the production of intracellular antibodies may be inhibited. However, in chronically uræmic patients the Mantoux test may be positive, implying that the formation of intracellular antibodies may also be maintained[3].

Since the principal response to orthotopic skin homografts occurs in the draining lymph nodes[5,6], the effect of acute uræmia on the regional lymph node reactivity to skin homografts has been investigated in 33 uræmic and 23 control rabbits. The animals used were adult females of albino and Flemish Giant strains. Animals from each strain were paired,

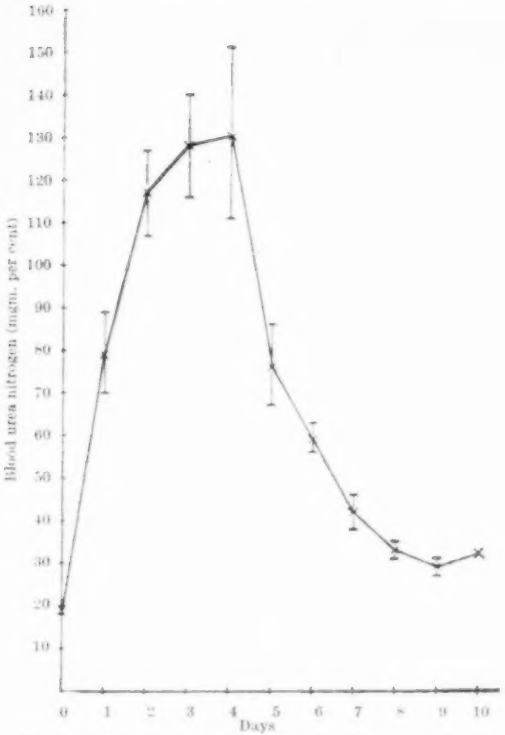

Fig. 1. Graph showing daily level of the blood urea nitrogen after occlusion of the right renal pedicle for 2 hr. Nephrectomy simultaneously performed on the opposite side

and under sodium pentobarbitone anæsthesia circular skin grafts 2 cm. in diameter were exchanged between the right ears. Acute uræmia was produced by means of unilateral nephrectomy, after which the pedicle of the other kidney was clamped for 2 hr.

Each day the grafts were inspected, the animals weighed and blood samples were taken from the left ears of the uræmic animals for blood urea nitrogen estimations. The animals were killed at intervals of time up to 14 days after operation. The parotid lymph nodes on the side containing the graft and on the contralateral side were removed, weighed and fixed in Carnoy's fluid.

The mean initial rejection-time of skin homografts exchanged between twelve healthy rabbits was 5·1 ± 0·9 days, whereas in eight uræmic animals, the mean initial rejection time was 10·8 ± 1·5 days. These observations have not been subjected to a *t*-test because the data are censored, implying that the sample of rejection times is not representative of the values which would have been obtained if all the rabbits had been allowed to live until the homografts were rejected. The criteria used for assessing the earliest signs of graft rejection were cyanosis, papillary congestion and intra-epidermal œdema appearing in skin which had shown evidence of survival. The blood urea nitrogen-levels in the uræmic group (Fig. 1) rose to a maximum between the fourth and the sixth day after grafting, and then fell rapidly towards normal levels. Two rabbits in which a secondary ante-mortem rise in blood urea nitrogen occurred have been excluded in the preparation of this graph. The mean absolute weight of the first regional lymph nodes draining the skin homografts at each time-interval after grafting in the control animals increased rapidly to a maximum by the sixth day after operation (Fig. 2), confirming the findings of Scothorne and McGregor[8]; the secondary rise in weight of lymph node after the tenth post-operative day was probably due to separation of the graft and infection of the graft bed. In the uræmic animals (Fig. 2) increase in the mean absolute weight of the first regional lymph nodes on the side receiving the graft was delayed until after the sixth day, by which time the azotæmia was returning towards normal levels (Fig. 1). A mean maximal weight was not reached until the tenth day, at about the time of graft rejection, which occurred at 10·8 ± 1·5 days. A secondary rise in weight of lymph node similar to that previously observed in the control group occurred after the twelfth post-operative day. Statistical analysis of the mean absolute lymph node weights between the uræmic and the control groups at each time interval has revealed a highly significant difference at the sixth ($P < 0.001$) and eighth ($P < 0.001$) days after operation.

Histological examination of first regional nodes draining tissue homografts has revealed the appearance of great accumulations of 'large lymphoid cells'[9–10] which reach a maximum between the fourth and sixth days after grafting[10]. The histological aspects of the present work will be reported in a further communication.

It is possible that acute uræmia exerts its effect of prolongation on skin homograft survival by a direct depression of the immunological reactivity of the lymph nodes draining the graft. However, the non-specific stress of the operation together with the acute uræmia may result in adreno-cortical stimula-

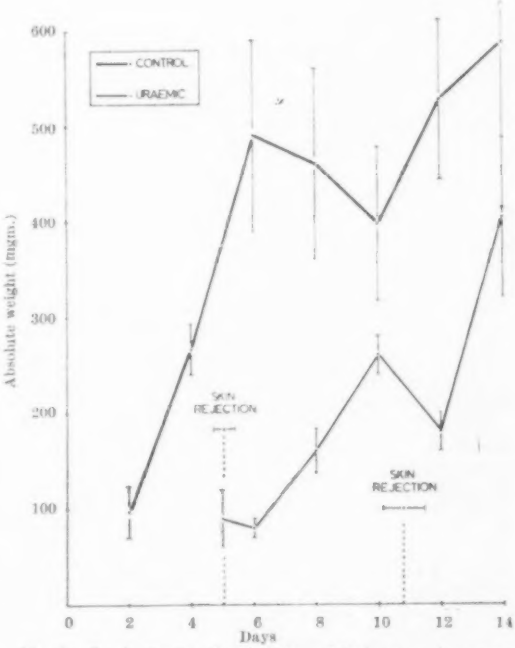

Fig. 2. Graph showing the absolute weight in mgm. (average value together with *S.E.*) of the parotid lymph node reacting to the presence of a 2-cm. orthotopic skin graft placed on the ventral aspect of the right ear. Control group above; uræmic animals below

tion. There is evidence to show that systemic or topical administration of cortisone acetate will prolong survival of skin graft in rabbits[11–13]. The possibility that the observed prolongation of skin homograft rejection time in rabbits with acute uræmia is due to adreno-cortical hyperfunction is being investigated at the present time. Further, the uræmic state of the recipient may inhibit the antigenicity of the homografted skin, a view which has been suggested as one of the ways in which cortisone may extend skin homograft survival[14]. An attempt was made to put the possibility of reduced antigenicity by uræmia to the experimental test, by grafting skin from severely uræmic rabbits on to six healthy rabbits. The mean initial rejection time of the skin homografts in this group of animals was 5·4 ± 0·5 days, a rejection time which is little different from the control group. Finally, Stoloff *et al.*[3] suggested that uræmia may act in prolonging homograft survival by diminishing the receptivity of the graft to the immune responses of the host. In the light of the impaired reactivity of regional lymph nodes draining skin homografts in the presence of acute uræmia, diminished receptivity of the grafts would seem unlikely to play anything more than a minor part in the extension of skin graft survival time produced by acute uræmia. A further and more detailed account of our findings will be given later.

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A New, Highly Effective but Non-Toxic Antibacterial Substance

We have discovered an entirely novel drug which is a polycondensed urea-formaldehyde having quite unexpected properties.

This polycondensate was found during a routine search for new classes of compounds with bacteriostatic properties. It is produced by a simple process of 'curing' a water-soluble pre-condensate of formaldehyde and urea units by high-temperature evaporation in a spray-tower at ordinary pressure and an alkaline *p*H. The resultant material is known as 'Anaflex', which is an amorphous white powder soluble to the extent of 0·28–0·31 per cent in water. It shows broad-spectrum bacteriostatic properties which are discussed here.

This product is a distinct entity, and differs from the well-known products resulting from 'curing' the water-soluble pre-condensates of urea formaldehyde with acid reagents at either high or low temperature as these are always devoid of any bacteriostatic activity.

Because of the low solubility of the new material it has proved difficult adequately to assess its physical constants. It is not crystalline and when heated it decomposes without melting.

Carbon–hydrogen–nitrogen analysis gives constant values, namely: C, 35·96; H, 5·88; N, 27·72; C, 35·68; H, 6·05; N, 27·76 per cent. This indicates $C_6H_{12}O_4N_4$ as a unit of the polycondensate molecule. $C_6H_{12}O_4N_4$ calculated gives: C, 35·29; H, 5·92; N, 27·44 per cent.

Both the oxygen and hydrogen content of the molecule is higher than would be expected from simple cross-linking of urea and methylene groups. We, therefore, feel that many free oxymethylene-substituents occur within the molecule and are responsible for the strong bacteriostatic activity.

This new material has been investigated to assess its effect as a bacteriocide against the following organisms:

Staphylococcus albus	*Salmonella paratyphosum A*
Staph. albus (penicillin insensitive)	*S. paratyphosum B*
Staph. aureus, coagulase positive	*S. paratyphosum C*
Staph. aureus, coagulase positive, type 43	*S.* mixed organisms
Staph. aureus, coagulase positive and penicillin and tetracycline insensitive	*S.*, local type
Strept. viridans (α-hæmolytic)	*Sh. dys. sonne*
Strept. pyogenes (β-hæmolytic)	*Sh. dys. schmidt*
Micrococcus tetragenus	*Lacto bacillus*
Strept. lactis (from fermented milk)	*N. catarrhalis sicca*
Pneumococcus	*N. catarrhalis*, smooth type
B. coli strain 1	*Alkaligenes alkaligenes*
B. coli strain 2	*Candida albicans*, type 1
B. coli strain 3	*Candida albicans*, type 2
Ps. pyocyanea, type 1	Unidentified yeast
Ps. pyocyanea, type 2	*Trichophyton*, type 1
Proteus morgani	*Trichophyton*, type 2
	C. diphtheriae
	C. hoffmani
	C. xerosis
	Aspergillus niger
	A. rubrum
	B. subtilis

Because of the low solubility in water the tests were carried out by Fleming's disk and ditch methods and the resulting zones of inhibition have been assessed.

In addition, in suitable liquid media which include 1 per cent glucose nutrient broth and modified brewer's broth, a suspension of 1 per cent of the new material w/v has shown similar inhibiting effects. Detailed tests have been made to eliminate bacteriostatic results by serial sub-dilutions in the appropriate media.

On serial sub-cultures of known micro-organisms from the periphery of the zones of inhibition repeated up to 100 times, no resistant strain of any of the test organisms has emerged. After these striking laboratory results the investigations have been extended to more than 200 human patients and these comprise at least:

40 cases furunculosis	7 fungal paronychia
20 ulcus cruris	9 athlete's foot
22 infected pressure sores	15 proctological cases
14 infected acne	20 cutaneous hypersensitivity
44 gynæcological discharges	11 axillary infections
14 napkin rash	2 seborrhœa capitis
20 infected industrial wounds	

Method of use. Clinically it only appears necessary to apply the medicament twice daily—preferably directly to the affected part—with a 'ring' of dressing to the circumambient areas to minimize secondary spread. In most cases occlusive dressings are contra-indicated.

The antibacterial spectrum is very wide, both *in vitro* and *in vivo*. It is not claimed that all the patients treated were cured; but it should suffice to indicate that more than 80 per cent of the furunculosis cases

were cured in less than 4 days. In cases where treatment was instituted within 48 hr. of the appearance of the initial lesions, these failed to develop into classical boils and the lesions disappeared in a further 48 hr.

A small comparative trial of nasal barrier creams was instituted. A well-known commercial cream containing chlorhexidine was used as the control. 'Anaflex' removed the infection from nasal carriers of penicillin-resistant *Staphylococcus* within 4–5 days; chlorhexidine produced a similar effect in 2–3 days but relapses occurred within 3 days. With 'Anaflex' relapses to the carrier state took at least 7 days.

It has proved in our hands extremely difficult to account for the mode of action of 'Anaflex'. It might be argued that it is due to a slow release of formaldehyde and indeed on treating this material with 4*N* sulphuric acid, 53 ± 1 per cent. formaldehyde is quantitatively liberated. But it has been found to be effective in urinary dermatitis (which has an ammoniacal basis). It is not possible to detect formaldehyde in the solution derived from 'Anaflex'. The distillate from such a solution is completely devoid of bacteriostatic effect and also of formaldehyde.

We have reason for believing that the bacteriocidal effects of the new material are enhanced by the presence of electrolytes and/or body proteins.

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HISTOCHEMISTRY

Cholinesterase in the Chicken Nervous System

WHILE making a topographical survey of the distribution of cholinesterases in the spinal cord and brain stem of the chicken in relation to the question of the selective neurotoxicity of certain organophosphorus compounds, we were led to make a comparison

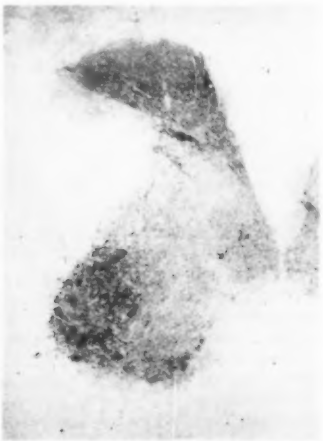

Fig. 1. Cervical spinal cord of guinea pig. Acetylthiocholine; Gomöri technique; *p*H 6·5; 2-hr. incubation

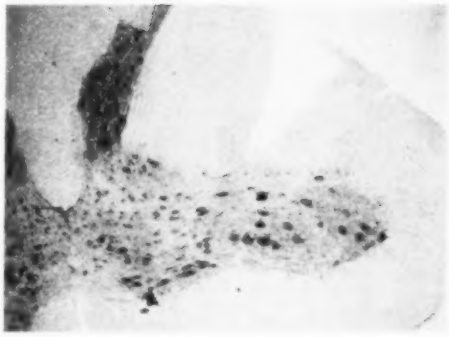

Fig. 2. Cervical spinal cord of chicken. Acetylthiocholine; Gomöri technique; *p*H 6·5; 2-hr. incubation

in four laboratory mammals (to be published). Koelle[1] had shown histochemically in the rat that considerable variation exists in the cholinesterase content of neurones from one centre to another. Hebb[2] also recognized in mammals neurones where the cholinesterase was for the most part intracellular (cholinergic) and neurones where it was largely distributed on the neuronal membrane (cholinoceptive). In contrast to this variability in mammals, the distribution of cholinesterase in chicken neurones is strikingly uniform.

All nerve cells of sensory ganglia, spinal cord and brain stem contain an abundance of this enzyme, and variation in content seemed to be related to neurone size. It is particularly interesting that the dorsal root ganglia cells are so active, for in mammals these cells are very poor in this enzyme while many contain none at all[3]. Hebb[2] likewise found that the second-order sensory cells in the cat were rich in enzyme, but not the primary cells. In the mammalian spinal cord (Fig. 1) cholinesterase is seen histochemically to be concentrated in the lateral and ventral regions and appears to be related both to neuronal surfaces and perikarya, the relative abundance at each area varying with the species. In the chicken relatively little is seen at cell surfaces, while all neurones show cholinesterase activity in their perikarya (Fig. 2). A similar constancy of distribution is found in the brain stem neurones.

On the other hand, certain richly synaptic zones such as the posterior horns of the spinal cord (Figs. 1 and 2), the descending root of the Vth nerve and certain cochleo-vestibular centres in the chicken contain an abundance of cholinesterase just as they do in the mammals examined. But the molecular layer of the cerebellum, which is also a richly synaptic area and also contains much cholinesterase in the chicken, is negative in the rat, rabbit and cat. In the guinea pig, however, it is almost as active as in the chicken.

If the presence of cholinesterase, shown in this work by its substrate and inhibitor characteristics probably to be true cholinesterase, is an index of the presence of a cholinergic transmission mechanism, then it would appear that the chemical transmission system of the chicken is probably of a simpler overall type than in higher species. On the basis of evidence, largely drawn from work on mammals, Hebb[4] has concluded that cholinergic transmission is probably not universal and is limited to only a proportion of cells, and that the rest must use some alternative chemical system for this purpose. It is

to be questioned whether these conclusions are in fact true for submammalian species or even whether absolute uniformity is to be expected among mammals as to which chemical system is employed in each region. Apart from the bearing that these findings have on the evolution of possible transmission systems, they emphasize the necessity for not drawing too close a comparison between the chicken and higher species when this animal is used for the purposes of experimental neurology.

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BIOLOGY

Sucker Display of *Octopus*

As a cephalopod, *Octopus vulgaris* is capable of the fastest and some of the most varied colour changes in the animal kingdom; yet there is a remarkable lack of evidence for these being used in courtship or mating displays of the kind associated with brightly coloured vertebrate animals. Courtship colour display by a less studied octopus (probably *O. horridus*) has been observed by Young[1], and the dramatic 'zebra' pattern of the decapod, *Sepia officinalis*, which is used both in courtship and as a threat between males, is well known.

Fig. 1. Photograph of a male (about 4 kgm.) displaying its suckers in response to a female approaching on its left side. The uppermost arm on the right of the photograph is arm 2 of the animal's left side; arm 1 left being held over towards the right side; arm 1 right is regenerating. Note the characteristic large suckers of the male on arms 2 and 3

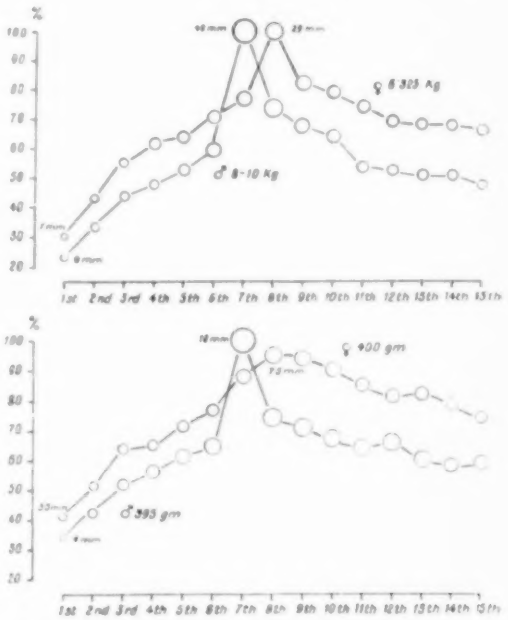
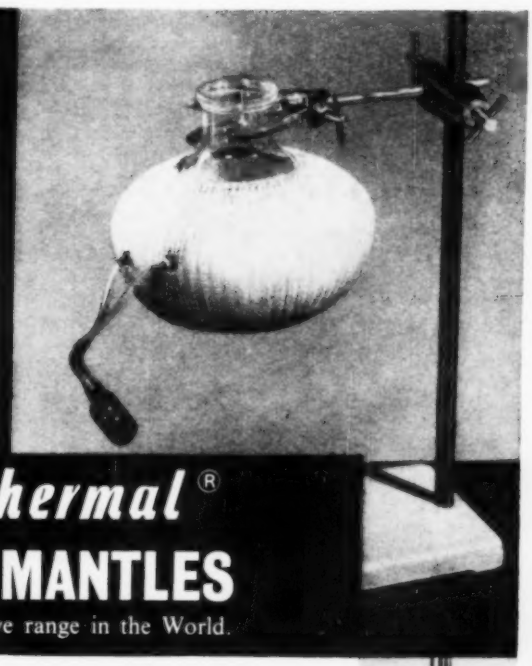

%
♀ 6.325 kg
♂ 8-10 kg
1st 2nd 3rd 4th 5th 6th 7th 8th 9th 10th 11th 12th 13th 14th 15th
%
♀ 900 gm
♂ 595 gm
1st 2nd 3rd 4th 5th 6th 7th 8th 9th 10th 11th 12th 13th 14th 15th

Fig. 2. Relative sizes of suckers at different levels on two males and two females of comparable weights. At each level outwards from the mouth the size of the sucker is given as a percentage of the diameter of the largest in the row. Plots are the average of measurements for single rows of suckers on arms 2 and 3 of either side. The diameters of the largest and of the most proximal suckers are indicated in millimetres. Measurements are from dead specimens

Reviewing the colour patterns of *O. vulgaris*, it soon becomes obvious that the well-known ones, for example, the dymantic 'startling' pattern described by Young, the deep reddening during an attack on a prey, and the various mottled patterns that clearly serve as protective coloration in different backgrounds, have an interspecific value rather than being intraspecific. The lack of information about colour patterns used intraspecifically may be due to the fact that the observer invariably takes part in an interspecific relationship with the animal and only rarely finds himself in a position to watch an intraspecific one. But a recent observation suggests that chromatophore colour patterns used in communication between one octopus and another may be of less importance than another signalling device, namely, the suckers.

During an encounter between one male *O. vulgaris* and a female in the Naples Aquarium, the male was seen to display its upturned arms while holding a position among the rocks from which it had just ousted the female. A photograph, taken at the time (Fig. 1), shows that certain suckers on the second and third arms of either side are larger than the others. It has not apparently been realized before, unless by Aristotle[2], that these are a regular external sexual character of the male *O. vulgaris* in addition to the hectocotylized tip of the third right arm. The presence of extra-large suckers at the level of the seventh or eighth pair, counting outwards from the mouth on arms 2 and 3 on either side, has now been found to be a reliable guide for the determination of mature males from females. At this level in both sexes the suckers, which increase in size outwards from



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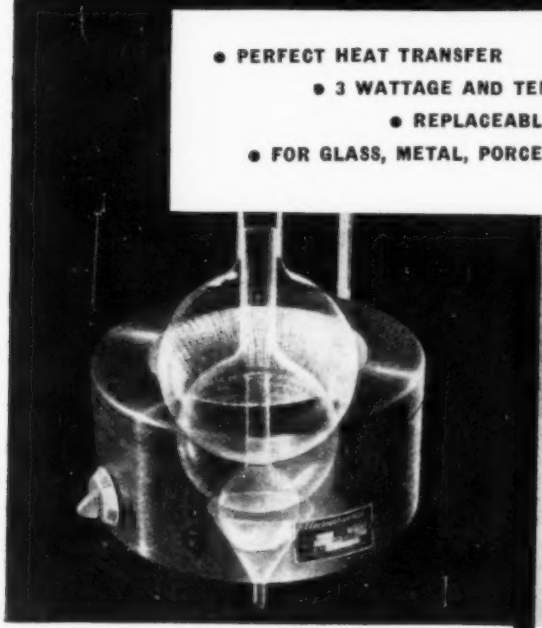

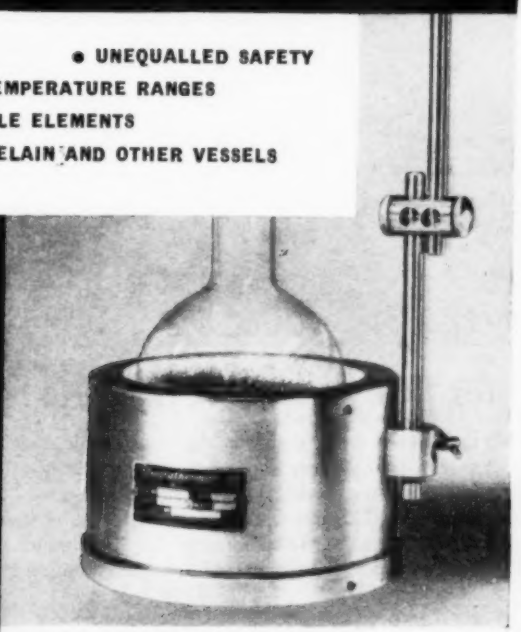

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the mouth, begin to decrease in size towards the arm tips, but in the male the largest sucker is proportionately larger than that in the female (Fig. 2).

A second observation made when a small but mature male was introduced to a female (four times his size) confirmed the impression that these large suckers are used as display between male and female. The body of the male was raised above the floor of the tank in such a way that the suckers near the mouth were showing with their undersides towards the female, and he approached with the third right arm outstretched in her direction. The proximal suckers were closed, by being folded on themselves, but the extra-large ones were, by contrast, expanded. Fig. 1 was taken at a moment when a female, attracted by a crab held close to the male, was approaching from the right of the photograph. It will be noticed that the closed suckers (here considered to be part of the complete display providing maximum contrast of expanded white on a dark ground) occurs on the side of the approaching female only. This is another example of unilateral response often observed in *Octopus* (also *Sepia*) when monocular vision is being used.

Another form of the sucker display used during copulation, and mentioned by Racovitza[3], has also been seen in the Naples Aquarium. While the male, sitting at right angles to the female, has his third right arm stretched into her mantle opening, the second right arm is curved back over the head so that the female is presented with a vertical double row of open suckers, the extra-large male suckers being the most conspicuous and directed with their expanded surfaces towards her.

Possible use of the sucker display by the male is as a recognition signal: male-to-female, especially important when the male is smaller than the female and might otherwise be attacked. Males mature at weights as little as 200 gm., females not until 2·5 kgm. or more[4], and it may be a normal requirement for small males to copulate with much larger females. To do so is to reverse the tendency of a small animal to withdraw from a larger one, as from a source of potential danger. A common feature of the withdrawal response of *O. vulgaris* is a turning up of the edges of the withdrawn arms so that the suckers, the surfaces of which are usually hidden by being in contact with the substratum, become visible especially on the stimulated side where the withdrawal proceeds further. This is often seen in training situations when animals are presented with a stimulus associated with punishment. In extreme withdrawal the arms are brought back over the head and mantle so that the suckers of all arms are visible. A film taken underwater of an octopus disturbed by a fish, shows very clearly how the moment in which the edges of the first arms are upturned, exposing the suckers, coincides with the closest approach of the fish, which then immediately halts and backs away. Such an interspecific display—as the movement clearly has become—develops directly from the protective withdrawal of the arms over the head. The sudden appearance of white circles, as upturning begins, startles the intruder.

The appearance to an octopus of white shapes on a dark background have for the past years been the subject of many experiments at Naples, and a white object such as a handkerchief or piece of plain cloth or white stone lowered into the water and dangled in front of an octopus has long been used by Neapolitan fishermen to lure an octopus out of its hole when no bait is handy or when other methods have failed. Boycott and Young[5] have considered the relative value as stimuli of rectangular and circular figures of the same area and Young[6] concludes that circles are attacked more readily than rectangles, while N. S. Sutherland (unpublished) has evidence that, of two different sized white circles presented together, the larger (within a diameter range of 2·7–5·6 cm.) is preferred even when attacks on both are rewarded.

The infundibular surfaces of the suckers are circular; they are white because the skin here lacks chromatophores: the outer keratinous layer of the skin of these surfaces is repeatedly renewed to maintain the efficiency of the suckers as adhesive organs. Therefore, given the existence of white circles as part of the anatomy of the animal and their visible appearance in only certain behavioural situations, it is not difficult to imagine that they should also have evolved a significance in communication, though we know almost nothing of how specific or capable of refinement this communication is.

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Movement of Coarse Fish in Rivers

IT is generally accepted[1] that coarse fish move to shallow water in the spring in order to spawn, and retire to deep water in the winter, but how extensive these movements are is not known. Work on American species has given rise to the concept of a 'home range'[2] which may be restricted to as little as a few 100 ft., and it has also been suggested that some species, including carp, are best regarded as having populations composed of mobile and sedentary fractions the relative proportions of which determine the degree of mobility shown by the species[3].

Investigations of coarse fish movements were made in the River Thames, near Reading, in 1959 and in the River Mole, in Surrey, between July and September 1960. The fish population in the Mole was repeatedly sampled by electric fishing at 14 stations, each about 200 ft. long, over a mile of the River. The catch, mostly roach and gudgeon, was marked either by fin clipping or by the attachment of a light metal tag, and released at the centre of the station in which it was caught. Altogether, 3,252 fish were marked over a period of five weeks and a total of 374 was recaptured during this period and a subsequent sampling period of two weeks.

The results showed no correlation between the time that fish had been at liberty and the distance travelled. Instead the frequency distribution of recaptures showed marked grouping about the point of release. In order to ascribe proper weighting to the distribution, the sampling effort exerted and the numbers of marked fish present have to be taken into account. The efficiency with which a station was sampled has been calculated as the fraction obtained by dividing the number of recaptured fish which were marked in the first week of the investigation by the

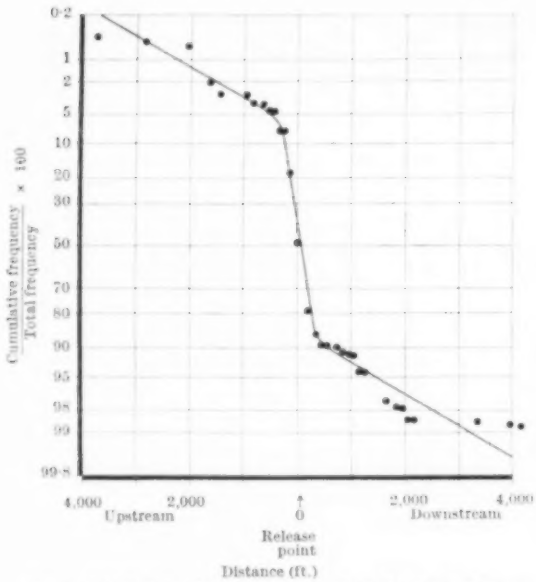

Fig. 1. Distribution of roach recaptures about the release point

total number of fish marked in the station during the first week. An analysis of variance showed that all samples could be regarded as having been taken with similar efforts. Therefore the weighting due to an individual recapture is given by :

$$\frac{1}{M_t.S_t}$$

where M_t is the number of marked fish present in the station of marking up to time t, and S_t is the number of samples taken up to and including time t at the station of recapture.

The corrected distribution is illustrated for roach in Fig. 1, where the cumulative frequencies are expressed as percentages of the total frequency and plotted on a probit scale against the distance from the station of marking. Using this method, a normal distribution gives a straight line with the slope of the line being a measure of the dispersal. However, in this case, a sigmoid curve is obtained which could be interpreted as the result of a combination of two normal distributions of differing dispersions. This seems to suggest that the roach population in the River Mole is made up of two components : a larger group comprising about 80 per cent of the individuals which remains within a range of 650 ft., and a smaller group of 20 per cent which moves more freely.

The weighting formula used introduces bias against recaptures showing no movement since M_t should be decreased by the unknown number which have left the station of marking. This makes the estimate of the proportion formed by the less-mobile group too low and its range too high ; but, since relatively few fish were taken outside the station in which they were marked, the differences will not be great.

The division of fish populations into two groups of differing mobility could provide an explanation of the apparently speedy recolonization of waterways by fish which, by the nature of their habitat, would be expected to exhibit station-holding behaviour.

Similar work is planned to investigate the movements of coarse fish throughout the year.

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Unilateral Implantation in the Uganda Kob

The Uganda kob, *Adenota kob thomasi* (P. L. Sclater), an antelope almost entirely endemic to Uganda, East Africa, inhabits primarily grassy plains along major rivers and lakes in the Western Rift Valley at elevations of 625–900 m. Its range extends approximately from 1° S. latitude to 4° N. latitude. Annual rainfall averages about 100 cm., and daily temperature varies approximately between 20° and 30° C. Breeding occurs throughout the year on special territorial grounds[1]. Gestation probably lasts about 7½ months, and normally the females are monotocous.

In the Semliki Game Reserve, 30 km. north of Fort Portal, Uganda, at 1° N. latitude, 150 mature female Uganda kob were collected. 12–15 individuals were shot each month during July 1957–June 1958. In addition, 10 females were taken immediately north of Murchison Falls National Park in the vicinity of Lolim Ranger Post. The position of the conceptus and distribution of cotyledons with respect to right and left horns of the bicornuate uterus were noted. Location of the most recent corpus luteum was recorded as to right and left ovary. Additional linear, weight and volume measurements were made of the uterus, extra-embryonic membranes and fluids, fœtus and ovaries. Analyses of these results are being prepared for publication. Samples of extra-embryonic tissues, ovaries, embryos, and fœtuses of less than 100 mm. crown-rump measurement were preserved.

Ovulation occurred at random between right and left ovaries (Table 1). In the tabulation, size of ovary is based on linear measurement, to the nearest millimetre, of the greatest three dimensions of the ovary prior to fixation. In pregnant females the larger size indicates the presence of a corpus luteum of pregnancy ; in non-pregnant females the larger size represents either a degenerating corpus luteum or an enlarged follicle. The present results support the principle of random distribution of ova released between right and left ovaries in monotocous species. Brambell[2] cites evidence for random distribution in the cow, sheep and monkey. Annual alternation between ovaries may occur, or there may be several successive ovulations from the same ovary. In the fur seal, *Callorhinus ursinus cynocephalus* (Walbaum), Enders *et al.*[3] found that a single ovum is ovulated annually from alternate ovaries, as shown by the persistent remains of the corpus albicans. The pattern of ovulation between right and left ovaries remains to be determined for the Uganda kob.

Implantation occurred uniformly in the right horn of the uterus, as indicated by the presence of the fœtus and the number of cotyledons in each horn (Table 1). Chorionic attachments to uterine caruncles occurred in the left uterine horn when growth of the conceptus was sufficiently advanced. Unilateral

Table 1. Frequency of Ovulation between Right and Left Ovaries; Number of Cotyledons in Gravid and Non-gravid Uterine Horns in Uganda Kob, *Adenota kob thomasi* (P. L. Sclater)

Phase of reproduction	No. of animals	Site of implantation		Larger ovary		Mean No. of cotyledons (range in parentheses)	
		Right	Left	Right	Left	Right horn (Gravid)	Left horn (Non-gravid)
Pregnant	116	116	0	57	59	14·0 (8–20)	7·6 (3–12)
Non-pregnant (lactating)	39	39	0	18	21	15·0 (10–21)	7·2 (5–10)
Non-pregnant (non-lactating)	5	5	0	2	3	15·0 (13–16)	7·0 (6–8)
Total	160	160	0	77	83	14·9 (8–21)	7·4 (3–12)

implantation appears to be a phenomenon that is unique in the Uganda kob. Since about 50 per cent of the ova are released from the left ovary, trans-uterine migration of the ovum or embryo must occur. This does not preclude the possibility of trans-peritoneal migration of the ova, although this route seems less likely. Trans-uterine migration has been recorded in the mink, *Mustela vison* Schreber[4]; the raccoon, *Procyon lotor* (L.)[5]; and the skunk, *Mephitis mephitis nigra* (Peale and Palisot de Beauvois)[6]. In sows, Hafez[7] found 41 per cent migration of ova on the basis of excess of ovulation sites over the number of implantations in the corresponding uterine horn. The physiological significance of unilateral implantation is not understood. E. M. Amoroso (personal communication) has shown that the distal portion of the uterus in the cat is more favourable for implantation than the proximal end. Possibly the endometrium of the right uterine horn provides the most favourable site for implantation in the Uganda kob.

One case (No. 47) of twins was discovered by W. O. Pridham, game ranger, Uganda Department of Game and Fisheries, immediately after parturition. Although the fawns (1 male and 1 female) were fully haired and approached mean parturition weight, they were dead. The female was shot while the extra-embryonic membranes were still retained in the uterus. At autopsy it was found that both foetuses had been in the right horn of the uterus, and two corpora lutea were present in the right ovary.

The results presented here were obtained during a Fulbright appointment to Uganda. I am indebted to Prof. E. M. Amoroso of the Royal Veterinary College (University of London) for encouragement in this work. A. C. Brooks, biologist of the Uganda Department of Game and Fisheries, transmitted Prof. Amoroso's ideas for field collection of the data and assisted with most of the field work. Eleven of the Uganda kob were collected by I. O. Buss, professor of wildlife management, Washington State University.

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Experimental Elimination of *Trypanosoma melophagium* Flu from its Hosts the Sheep and the Ked, *Melophagus ovinus* (L.)

Trypanosoma melophagium Flu is a non-pathogenic parasite of sheep, and its intermediate host is the sheep ked[2]. The parasite is world-wide in its distribution and is found wherever there are keds[1]. Infection of sheep usually takes place via the oral mucosa following ingestion of infected keds[2,3]. If sheep are treated to destroy keds, it is several months before the flagellates disappear from the host's blood. I[2] reported the death of large numbers of keds due to blockage of the midgut by masses of crithidia. Control over the trypanosome infection would be a useful tool for investigating this phenomenon further. The organism is not trans-ovarially transmitted in the ked[2] and thus flagellate-free insects should be easy to obtain.

Infected populations of keds on sheep were destroyed by spraying with 0·5 per cent toxaphene or malathion 6–8 weeks in advance of experiments to avoid residual toxicity to keds.

A week before re-infestation, sheep were given quinapyramine sulphate ('Antrycide', Imperial Chemical Industries, Ltd.), 8 mgm./kgm. subcutaneously. Sheep were infested with puparia which had been disinfected in 1 per cent mercuric chloride. Effectiveness of the drug in suppressing trypanosomes in the blood was checked weekly by dissecting 4–6 keds from each animal, wet-smearing the posterior midgut beneath a coverslip, and examining for crithidia under high dry magnification.

Lower doses of 'Antrycide' were not completely effective, and infection appeared in some keds within a few weeks. Higher doses caused toxic symptoms and occasionally death in sheep. At 8 mgm/kgm., trypanosome-free units can be maintained for several months provided there is no opportunity for re-infection. Sheep should be housed separately in clean quarters which have not recently contained infected animals. Even when trypanosome-free sheep were kept 50 ft. from infected sheep in the same barn, infection appeared in keds within a few weeks. This suggests that the infective forms present in ked faeces may be air-borne and may enter the sheep via the respiratory mucosa as well as by the oral route.

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Culicoides adersi Ingram and Macfie, 1923, a Presumed Vector of *Hepatocystis* (= *Plasmodium*) *kochi* (Laveran, 1899)

Monkeys of tropical Africa are well known to harbour a malaria parasite *Hepatocystis* (= *Plasmodium*) *kochi*, characterized by the presence of gametocytes only in the blood, and by the occurrence of schizogony in the form of macroscopic merocysts in the liver. As a malaria parasite, its vector was suspected for a long time as being a mosquito and several attempts were made experimentally and in Nature to incriminate these insects[1,2]. All failed, not altogether unexpectedly, when it was shown[3] that the parasite

Table 1. Attempts to infect Monkeys with Sporozoites from *Culicoides adersi*

Species of monkey	Serial No.	Inoculum	Route	Date	Result	Remarks
aethiops	35	15 positive glands	Subcutaneous	4.9.60	Negative for 7 months	Suspensions ? viable
aethiops	28	27 positive glands	Subcutaneous	28.9.60	Monkey died after 1 month; negative	Suspensions ? viable
aethiops	50	16 positive glands	Subcutaneous	30.9.60	Negative for 6 months	Suspensions ? viable
aethiops	30	4 positive midges	Bite	28.9.60	Gametocytes appeared on 1.2.61	
aethiops	31	Suspension of 60 midges (heavily positive batch)	Intravenous	6.1.61	3	Garnham technique
rhesus	23	Suspension of 21 midges (heavily positive batch)	Intravenous	7.1.61	3	Garnham technique

belonged not to the family Plasmodiidae but to the Haemoproteidae in which the sporogonic cycle was known to take place in *Simulium*, *Culicoides* and hippoboscids, but never in mosquitoes. The search was therefore widened to include other arthropods and a range of species was examined[3], but again with negative results. There was a slight indication that midges might be concerned, and in July 1959 an attempt was made to test this hypothesis in East Africa in a place where the monkeys were heavily infected with the parasite. We selected Port Reitz on the mainland near Mombasa, and worked at a small field laboratory conveniently situated in the middle of the area.

Heavily infected *Cercopithecus aethiops* monkeys were obtained, anæsthetized with 'Sernyl' (Parke Davis) and exposed to the bites of *Culicoides adersi* at dawn and dusk in the mangrove swamps, where these insects abound during the spring tides. Simultaneously, *C. adersi* were allowed to feed on human bait, and all the specimens were kept singly in tubes 2 in. × ½ in. at a relatively uniform temperature (about 80° F.) in the laboratory. They were supplied with dilute glucose solution from the second day onwards on filter paper 'wick'.

Ookinetes were found in smears of the gut contents 20 hr. after the infective feed, but at first no later stages were detected. Then in August 1959 one of us (M. I.) found sporozoites in the salivary glands of a midge which had fed on an infected monkey 13 days before. Later dissections revealed a high rate of infection in the experimental insects, but a much lower incidence in the controls which had fed on man. Thus during August 1959–January 1961, the salivary glands and guts of 1,928 *C. adersi*, which had fed on an infected monkey 5–15 days previously, were examined and 568 or 29·5 per cent were found to show sporozoites. At the same time, 247 control midges which had fed on man 5–15 days previously were examined and 4 or 1·6 per cent were found to contain sporozoites. All these insects were caught in the wild, and an infection-rate of 0·2 per cent (4 in 2,400) was found in unfed specimens, dissected on the day of capture.

The sporozoites were curved bodies, about 13μ in length, and usually had a single, solid bead-like nucleus, often placed nearer the pointed end of the sporozoite; the other end was blunt. In serum Locke fluid, the sporozoites showed a peculiar type of movement, one-half contracting with a snake-like motion, yet rather jerkily.

The sporozoites were first detectable in small numbers around the mid-gut and Malpighian tubules 5 days after an infective feed; they tended to increase during the sixth and seventh days when the salivary glands became invaded. Infection persisted in the glands for at least 17 days, but declined in intensity after the thirteenth day. It was difficult to be sure about the latter point, because the majority of infections at any time were light; it was quite exceptional to find, for example, several hundred sporozoites.

Attempts were made to transmit the infection to clean monkeys and the results are shown in Table 1. A vervet monkey (No. 30) was bitten by four midges on September 28, 1960; the salivary glands were then extracted and all four were found to contain sporozoites. The blood of the monkey was examined twice a week until February 1, 1961, when parasites were first detected. There is thus a pre-patent period of four months.

Many of the batches of midges which had fed on *kochi*-infected monkeys were found to be infected in a range of 60–90 per cent, while controls fed on man were almost entirely negative (4/247). We have sought in vain for any explanation other than the obvious one that the midges were acting as vectors of *H. kochi*.

The experiments were tainted because we were compelled to use wild-caught flies, and they are therefore subject to the criticism that the sporogonic cycle may have had an extrinsic origin. If so, what could this have been? *Culicoides* spp. have been shown to be the natural vectors of *Haemoproteus* in Canadian birds[4] and we found *Haemoproteus* in weaver birds in the mangrove swamps where we were working. Nevertheless, if the sporozoites had been of avian origin, the infection-rate in the controls should have been similar to that in midges fed on monkeys, but instead of 60 or 70 per cent it was 1·6 per cent, while in unfed wild-flies dissected on the day of collection, the incidence was 0·2 per cent. Keeping the flies for a week or longer would, of course, allow natural infections to mature and the rate would increase accordingly (that is, to 1·6 per cent). It is, therefore, probable that the natural rates represented true *H. kochi* infections acquired in the field, because monkeys are said to descend from the second growth forest, scrub or plantations to the mangrove swamps by the creeks, where they would be attacked by midges.

The rapid cycle of sporogony (5 days), the low production of sporozoites, their gradual release from oöcysts, and the small size of the oöcyst, are all features[5] of the developmental cycle of two other common members of the family—*Leucocytozoon* and *Haemoproteus*, and as *Hepatocystis* belongs to this family (Haemoprotedae) it is not surprising that it also should exhibit all or most of these features. Canadian workers took a long time to identify with certainty the oöcysts of both *Leucocytozoon* and *Haemoproteus*; they are much smaller than in *Plasmodium* and it is not altogether surprising that, so far, we have been unable to find them in *Hepatocystis*.

Slight differences can be seen in the sporozoites of the different genera as follows: *Leucocytozoon*, 9–13μ in length; more pointed at one end. *Haemoproteus* (*Culicoides* type), 10–14μ; ends similar.

Haemoproteus (*Lynchia* type), 9μ or less; more pointed at one end. *Hepatocystis*, 13μ; more pointed at one end. *Plasmodium*, 10–14μ; ends similar.

The morphology of the sporozoite found in *C. adersi* is another indication that they are not *Haemoproteus*. The vector of *Leucocytozoon* is a *Simulium* which, presumably, excludes this organism from the argument.

We were afraid at first that Koch's '*Plasmodium*' was not going to conform with his 'Postulates'; the monkeys which were inoculated with sporozoites from slide preparations of glands are still negative, but the monkey which was bitten by infected *Culicoides* has now, after 4 months, become positive. The tissue forms of *Hepatocystis* have a diameter of about 40 times that of a liver schizont of *Plasmodium*; the pre-patent period of the latter is 5–10 days, so it is scarcely surprising to find that it takes nearly that number of months for *Hepatocystis* to mature in the liver.

We report these findings in the belief that the midge is the vector of *Hepatocystis*, and in the hope that similar experiments will be made elsewhere in the Old World where species of *Hepatocystis* are common in various animals.

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Azulene Derivatives as Plant Growth Regulators

Among the many hundreds of compounds examined for effects in promoting cell elongation, very few having activity do not have a ring structure possessing aromatic character[1]. Thus it is logical to look for activity in compounds having 'non-classical' aromatic rings such as derivatives of azulene and ferrocene. The azulene compounds are of particular significance since this ring system occurs frequently in essential oils and plant tissue, and anti-inflammatory, anti-allergic, bacteriostatic, cancerostatic and anti-arthritic activities have been claimed for azulenes[2].

Ferroceneacetic acid, ferrocenediacetic acid and ferrocenepropionic acid are all completely inactive in cell elongation as shown by their lack of effect on 3-mm. segments of *Avena* coleoptiles[3]. However, as shown in Table 1, some azulene derivatives have high activity in promoting cell elongation. Since azulene compounds are isomeric with corresponding naphthoic compounds, it would be expected that a similar pattern of activity would be found in the two series and the lack of activity of azulene-1-carboxylic acid

Table 1. Percentage Elongation of Coleoptile Segments in Solutions of Azulene Derivatives and Naphthoic Acid as compared with Percentage Elongation in Water

	Molar concentration			
	10^{-4}	5×10^{-4}	10^{-3}	5×10^{-3}
Azulene-1-acetic acid	0	+12	+22	+31
Azulene-1-acetonitrile	+8	+17	+16	+11
Azulene-1-carboxylic acid	0	0	0	−8
1-Naphthoic acid	0	0	0	0

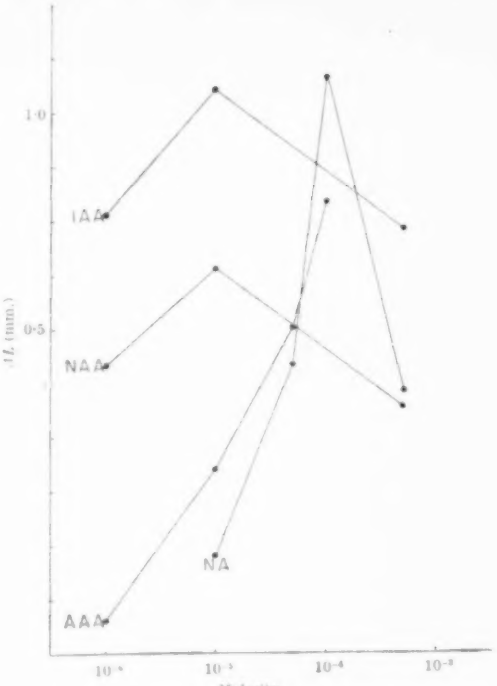

Fig. 1. Growth in length induced by indole-3-acetic acid (IAA), α-naphthaleneacetic acid (NAA), azulene-1-acetic acid (AAA) and 1-naphthoic acid (NA) of segments of pea stem tissue

and 1-naphthoic acid in coleoptile tissue[4] is in agreement. However, many reports have assigned activity to 1-naphthoic acid in pea tissue[4–6] and it was, therefore, of interest to examine the effects of the azulene compounds on elongation of 5-mm. segments of stem tissue of pea. Azulene-1-carboxylic acid does not promote elongation in pea tissue although 1-naphthoic acid is very effective as shown in Fig. 1. This finding demonstrates a difference in the plant substrate in pea tissue and *Avena* coleoptile tissue. Whether the difference in activity of the azulene-1-carboxylic acid and 1-naphthoic acid is the result of a steric or electronic difference in the 7- and 6-membered rings remains to be established. Although azulene-1-acetic acid and 1-naphthoic acid at low concentrations have much less effect on elongation than indole-3-acetic acid or α-naphthaleneacetic acid, at high concentrations their effects become equivalent.

Azulene-1-acetonitrile is totally inactive in promoting elongation of pea tissue and is thus similar to indole-3-acetonitrile, which the pea tissue, unlike *Avena* coleoptile tissue, is unable to convert to the active acid[7].

It is difficult to decide how much activity should be expected for azulene-1-acetic acid in comparison with α-naphthaleneacetic acid. According to the two-point attachment hypothesis[1,3,6,8] such growth regulators react with an electron-rich point on a plant substrate through a position on the ring which is ortho to the carboxyl group of the regulator. It is well known that the 8-position in azulene is very susceptible to attack by electron-rich reagents, and high activity of azulene-1-acetic acid is therefore not

surprising. Reactivity indices (approximate super-delocalizability) calculated by Koshimiza, Fujita and Mitsui[6] according to the frontier electron theory[7] indicate that the 8-position in 1-naphthoic acids is the site of reaction on the ring. Evidence for the involvement of the 8-position of azulene compounds in the reaction also exists in the sterically similar naphthalene situation where the 8-position seems more important than the 2-position, as Burstrom *et al.*[8] have shown 8-chloronaphthalene-1-acetic acid is much less active than α-naphthaleneacetic acid even though chlorine is normally an activating group. Whether or not the small activity at low concentrations is the result of the greater instability of the azulene ring or some basic structural unsuitability of the molecule is unknown.

The fact that the non-alternate aromatic system, azulene, is active in promoting elongation suggests that other such systems should be investigated.

We are indebted to Prof. Arthur G. Anderson, jun., of the University of Washington, for the azulene derivatives examined in this investigation, and to Prof. Kenneth L. Rinehart, jun., of the University of Illinois, for the ferrocene derivatives.

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ENTOMOLOGY

The Function of the Paleal Pegs of Corixidae (Hemiptera Heteroptera)

The Corixidae are a family of aquatic bugs living on the habitat bottom. The front legs of both sexes are used for collecting food, the tarsi (or paleæ) being highly specialized for this purpose. The middle legs have retained their ambulatory form, and the long claws are used for anchoring the insect to the habitat bottom during feeding. The hind-legs are used for swimming, the tibiæ and tarsi being specially flattened for this purpose.

The front legs sweep a food-bearing water current towards the mouth by means of the longitudinal rows of setæ on the paleal edges (Fig. 1, *c* and *d*). In the males, the inner surface of each palea bears a longitudinal row of pegs, which is represented in the female by a row of short setæ (cf. Fig. 2 and Fig. 1, *b*). Kirkaldy[1] suggested these pegs were used for stridulation; but the work of von Mitis[2] has shown that sound is produced in other ways. The form of the male paleæ and the arrangement of the pegs is fairly constant for each species and these features have been used for species identification in British taxonomic works by Saunders[3], Butler[4], Macan[5] and by Southwood and Leston[6].

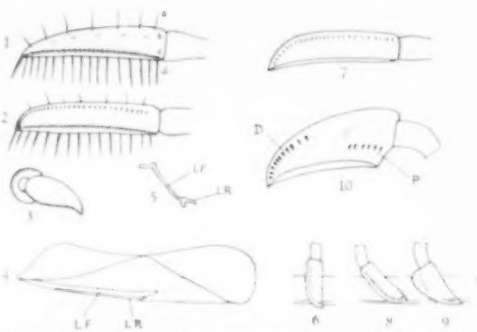

Fig. 1. Median surfaces of the tarsus and tibia from the front right leg of *Corixa punctata* (female). Fig. 2. Median surfaces of the tarsus and tibia from the front right leg of *Corixa punctata* (male). Fig. 3. Enlarged view on a paleal peg of *C. punctata*. Fig. 4. Hemielytron of *C. punctata*. Fig. 5. Enlarged view of a transverse section of the lateral flange to show outer ridges. Fig. 6. Left leg and lateral flange of *H. sahlbergi* during copulation. Fig. 7. Median surface of the tarsus and tibia of the front leg of *H. sahlbergi* (male). Fig. 8. View of left leg and lateral flange during copulation of a hypothetical species with a curved tibia. The paleal pegs would not grip the ridges of the lateral flange. Fig. 9. Lateral view of left front leg and lateral flange of *Sigara distincta* during copulation. Notice the distal row of paleal pegs is rotated to grip the flange ridges. Fig. 10. Median surfaces of the tarsus and tibia of *Sigara distincta* (male). (In Figs. 6, 8 and 9 the paleal pegs are drawn as though they could be seen through the palea.)
a, *b*, *c*, *d*, rows of paleal setæ; *D*, distal row of paleal pegs; *LF*, lateral flange; *LR*, longitudinal ridge of lateral flange; *P*, proximal row of paleal pegs

The true function of the paleal pegs may be observed during copulation. When mating, the male darts on to the back of the female which he holds by pressing his head against her pronotum—the frons of the male being flattened or even concave for this purpose. In addition the front legs are stretched sideways and the inner surface of each palea is extended over the lateral flange of the hemielytron on the corresponding side (Fig. 6). The paleal pegs are composed of a circular base on which is a short peduncle supporting a larger conical structure. The cone is not vertical, but bent towards the centre of the palea (Fig. 3). The lateral flange of the hemielytron (Fig. 4) is slightly concave in transverse section and the outer margin is raised into a longitudinal ridge, which in the region of the metathorax is enlarged and folded outwards to form a longitudinal grip (Fig. 5). When the front legs of the male are extended sideways, the distal pegs become caught under the curved longitudinal ridge of the lateral flange on the hemielytron and the two sexes are thus able to swim and surface while firmly attached to one another in this way.

In *Corixa punctata* (Illig.) the paleal pegs form a single row, which is curved distally to run slightly transversely across the palea (Fig. 2) and this appears to be a primitive arrangement in the Corixidae. Primitively the tibia is straight; but in the more specialized species tends to become curved inwards to aid food-collecting. If the paleal pegs retained their primitive arrangement, their effectiveness in holding the female would be reduced (Fig. 8), but changes in the tibia are associated with a broadening of the male palea and the row of paleal pegs is distally rotated so as to retain the original relationship with the hemielytral ridges. As a result of these changes, the row of paleal pegs tends to become broken into a distal functional row and a proximal row in which the pegs tend to become vestigial. These changes are well illustrated by a comparison of *Hesperocorixa sahlbergi* (Fieb.) (Fig. 7) and *Sigara distincta* (Fieb.) (Fig. 10).

At first sight the form of the male palese and the arrangement of the paleal pegs would appear to be non-adaptive; any one arrangement of paleal pegs being as effective as any other for gripping the female. But the front legs are used for other functions, particularly feeding, and a study of the functional morphology of the front legs shows that the form of the male palese and the arrangement of the pegs is of great functional significance, as well as being a valuable taxonomic feature at the species-level.

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Atypical Spermiogenesis in *Thermobia domestica*, a Thysanuran Insect

In a recent communication, Bawa[1] has again put forward the hypothesis of a typical sperm in *Thermobia domestica*. However, I have shown[2], with some electron photographs of *Petrobius maritimus*, that the centriole and the acrosome are in their normal positions. The acrosome is a scoop-shaped body at the anterior end of the nucleus which forms a projecting tube. What Bawa has called the acrosome is probably another body, the centriole adjunct[3], which encloses a centriole and gives rise to the flagellum. In Thysanura, no division of the centriole occurs, and as such it is a fixed body on the posterior aspect of the nucleus. These observations are further strengthened by the detailed cytochemical reactions obtained by me, the results of which will be published elsewhere.

As regards the 'adnuclear fold' or the 'lateral fold', it is very clear from the electron photographs that the fold is not a continuation of the flagellum as it does not possess the typical fibrillar structure. On the contrary it is an intra-nuclear body of unknown significance. This body is an easily followed structure in X-irradiated *Petrobius*[4]. It also differs with the flagellum in chemical constitution.

Finally, I again stress that the sperm of thysanuran is a typical flagellate sperm and does not show any deviation from the normal patterns.

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MATHUR (preceding communication and ref. 1), in his communications, has again stressed that the thysanuran sperm is a typical flagellate one, having the acrosome and the centriole located at the proximal and distal end of the nucleus. I disagree with him and have the following comments to make in this context.

Mathur's[1] report is incomplete inasmuch as he does not mention (1) the name of the insect, (2) the stage of spermiogenesis electronmicrograph 1 represents and (3) the magnification of the two electron micrographs. I may add that I am unable to interpret his electronmicrograph 2. Furthermore, if I am interpreting correctly, Mathur's electronmicrograph 1 is a spermatid of a thysanuran. After scrutinizing scores of electronmicrographs of *Thermobia* spermatids[2], it is safe to point out that Mathur's acrosome *A* is actually the nucleus which shows nuclear pores at places, and his nucleus *N* is unmistakably a typical mitochondrial nebenkern revealing badly damaged cristæ. Mathur, however, does not mention anything about the mitochondria. It has been reported[2] that a typical mitochondrial nebenkern is formed in *Thermobia* and other thysanurans, and it remains an integral part of the mature spermatozoan. The structures F_1, F_2 and F_3 in Mathur's[1] electronmicrograph 1 do not reveal any structural detail to be identified as parts of the flagellum cut at different places. He also fails to make reference to bodies labelled as *M* in electronmicrograph 1. It is not clear whether bodies *F*, *M* identified by him in the upper right corner of electronmicrograph 1 are inclusions in the same cell referred to in the micrograph or are located in an adjacent cell. Structures *CA*, *M*, F_1, F_2 and F_3 probably are the microbodies or lipid elements, as such inclusions are invariably observed in the spermatids of *Thermobia*. So far as I can understand, the only structure identified correctly by Mathur[1] in electronmicrograph 1 is the Golgi material, *G*.

In *Pterobius* spermatid, Gatenby and Mathur[3] using light microscopy were unable to establish the correct nature of the 'adnuclear' or 'lateral fold'. This structure, according to Mathur, is the 'intranuclear' body of unknown significance. However, this 'intranuclear body' is seen to consist of the tail flagellum and the two mitochondrial nebenkern ribbons[1,4,5]. Electron microscopy[2] of *Thermobia* clearly indicates the composite nature of this intranuclear body. In favourably cut ultra-thin sections of *Thermobia* spermatids, one can discern tail filament complex and the mitochondrial cristæ in the nebenkern ribbons. It is important to mention also that the nucleus, mitochondrial nebenkern and the tail filament complex are seen to be disposed adjacent to each other. Such a unique spatial arrangement is especially clear in the cross-sections. Finally, there is evidence[2] that the acrosome occupies the basal end of the sperm head and that it is derived from the Golgi dictyosomes. The centriole is not embedded in the 'centriole adjunct' and it moves around the nucleus until it lies toward the apical end of the nucleus. Thus there is no reason to confuse the 'centriole adjunct' of Gatenby *et al.*[6] with the acrosome of *Thermobia domestica* spermatozoan.

This work was supported in part by the Population Council, Inc., New York.

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GENETICS

Mitotic Haploidization by Treatment of *Aspergillus niger* Diploids with *para*-Fluoro-phenylalanine

In genetic analysis based on mitotic segregation[1-4] an important step is the recovery of haploid segregants from heterozygous diploids. This has been done until recently by laborious or complicated techniques[4,5]. I am indebted to Dr. G. Morpurgo, of the Istituto Superiore di Sanità, Rome, for informing me and permitting me to make use of his discovery that treatment with *para*-fluoro-phenylalanine of diploids of *Aspergillus nidulans* leads to wholesale segregation (this discovery was made known in the privately circulated *Aspergillus News Letter*, p. 10, No. 2, Spring 1961). In an extensive work expanding the formal genetical analysis—via mitotic segregation—of the fungus *A. niger*[6], I have applied this treatment to diploids of this asexual species.

The amino-acid analogue DL-*para*-fluoro-phenylalanine was incorporated in standard complete medium[7] to a final concentration of 1/10,000 w/v and conidia from diploid strains heterozygous for a number of colour and nutritional markers were plated on the surface. At this concentration of the analogue, the viable counts remain the same as on standard complete medium, but the rate of growth is much slower (diameter of colonies after 5 days: 0·5–1 cm. instead of about 10 cm.) and sporulation is very poor. These colonies produced sectors, the rate of growth and sporulation of which was about the same as on normal complete medium. After 10 days, conidia of these sectors were streaked on complete medium, classified for ploidy on the basis of the diameter of their conidia and tested for requirements. All of them turned out to be haploid and of all possible recombinant types between independent markers.

As an example, a heterozygous diploid with black heads (wild-type) and prototrophic was synthesized from two haploid strains: one fawn (*a*) and the other olive (*o*) (two recessive non-allelic markers belonging to the same linkage group). The two strains also differed in four recessive nutritional requirements and the genotype of the diploid formed from them was:

a	+	+	+	gua_7	$meth_7$
+	*o*	*hist*	lys_4	+	+

The vigorously growing sectors produced by this diploid were either fawn or olive. To minimize clonal effects, only one sector of each colour (fawn or olive) was picked from a colony. The 74 sectors so isolated, 38 fawn and 36 olive, fell into the 8 possible classes of segregants and recombinants in respect of the four other markers belonging to three different linkage groups.

That haploidization, as a consequence of *para*-fluoro-phenylalanine treatment, occurs by successive losses of chromosomes—as found by Käfer[4] for *Aspergillus nidulans* in the case of 'spontaneous' haploidization—is shown by the following evidence: The results just mentioned are obtained by isolating vigorously and well-sporulating sectors from diploid colonies grown in the presence of the analogue for ten days. If small groups of hyphal tips are taken from diploid colonies only after 48 hr. of growth in the presence of the analogue and transferred to normal medium, they produce sectors in which more and more nutritional markers segregate as growth proceeds. On *para*-fluoro-phenylalanine the amount of growth intervening between the original diploid mycelium and the completely haploid sectors is relatively small, indicating a selective effect against diploids and disomics. I interpret this to mean that loss of individual chromosomes in a haploid leads to no further divisions of that nuclear lineage, while in a diploid or disomic stunted growth may go on.

The availability of a treatment which produces wholesale haploidization is a very valuable addition to the techniques for genetical analysis via mitotic segregation.

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Hybrids between *Solanum bulbocastanum* and *Solanum cardiophylium*

The Mexican diploid tuberous *Solanum* series Bulbocastana and Cardiophylla are important potential sources of genes for resistance to late blight of potatoes. Niederhauser and Mills[1] noted field immunity in certain clones of *S. bulbocastanum* in their field trials in Mexico. No investigator has hitherto reported hybrids between these series and the Tuberosa. A knowledge of the crossability relationships of the Mexican diploid species may be useful in overcoming their apparent isolation.

Extensive collections were made of *S. bulbocastanum* Dun. and *S. cardiophyllum* Lindl. throughout their ranges in Mexico during 1956 and 1957. The collections of *S. cardiophyllum* were comprised of *S. cardiophyllum sensu stricto*, *S. ehrenbergii* (Bitt.) Rydb. and *S. cardiophyllum* var. *endoiodandrum* Bitt. Seed set occurred from crosses between *S. bulbocastanum* (C-238) and *S. cardiophyllum* (C-297), and in the reciprocal cross between *S. ehrenbergii* (C-370) and *S. bulbocastanum* (C-194).

The hybrid plants from both crosses showed in their seedling stages the unifoliate characteristic of the *S. bulbocastanum* parent. As they approached the flowering stage, they presented the aspect of a compound-leaved *S. bulbocastanum*.

Although the hybrids produced a high percentage of stainable pollen, it was not always possible to obtain fruit and seed set by sibling pollinations within the families *C*-238 × *C*-297 and *C*-370 × *C*-194. The inter-family cross-pollinations attempted were successful in both directions. This observation suggests a repetition of the intra-family cross-incompatibility noted by Graham *et al.*[2] in *S. bulbocastanum*.

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FORTHCOMING EVENTS

*(Meetings marked with an asterisk * are open to the public)*

Tuesday, May 23

UNIVERSITY OF LONDON (at Imperial College of Science and Technology, London, S.W.7), at 5.30 p.m.—Prof. B. G. Neal: "Some Problems in Plasticity" (Inaugural Lecture).

SOCIETY OF CHEMICAL INDUSTRY, PLASTICS AND POLYMER GROUP (in the Film Theatre of Shell-Mex House, Strand, London, W.C.2), at 6 p.m.—Annual General Meeting. Mr. P. S. Adamson: Chairman's Address.

SOCIETY OF INSTRUMENT TECHNOLOGY (at Manson House, 26 Portland Place, London, W.1), at 6 p.m.—Annual General Meeting, 7 p.m.—Presidential Address.

Wednesday, May 24

LINNEAN SOCIETY OF LONDON (at Burlington House, Piccadilly, London, W.1), at 5 p.m.—Anniversary Meeting. Prof. C. F. A. Pantin, F.R.S.: "On the Teaching of Biology" (Presidential Address).

EUGENICS SOCIETY (at the Royal Society, Burlington House, Piccadilly, London, W.1), at 5.30 p.m.—Prof. C. D. Darlington, F.R.S.: "Cousin Marriage".*

SOCIETY OF CHEMICAL INDUSTRY, FOOD GROUP (at 14 Belgrave Square, London, S.W.1), at 6.15 p.m.—Annual General Meeting, followed by Mr. T. McLachlan: "Some Historical Notes on Food Technology".

BRITISH PSYCHOLOGICAL SOCIETY, MEDICAL SECTION (at the Royal Society of Medicine, 1 Wimpole Street, London, W.1), at 8.30 p.m.—Symposium on "The Saboteur in Group Psychotherapy". Speakers: Dr. Malcolm Pines, Dr. Robin Skynner and Dr. S. Resnik.

Thursday, May 25

ROYAL SOCIETY (at Burlington House, Piccadilly, London, W.1), at 4.30 p.m.—Sir Charles Darwin, F.R.S.: "The Gravity Field of a Particle. II". Mr. B. Thwaites: "The Aerodynamic Theory of Sails. I. Two-dimensional sails".

INSTITUTION OF MINING AND METALLURGY (at the Geological Society, Burlington House, Piccadilly, London, W.1), at 5 p.m.—Mr. K. R. Hyde, Prof. P. L. Robinson, Mr. M. J. Waterman, and Dr. J. M. Waters: "Reaction of Beryl with Sodium Fluorosilicate Used in Extracting Beryllium from the Mineral"; Dr. J. S. Tooms and Mr. S. Kaewbaidhoon: "Dispersion of Tin in Soil over Mineralization at Sungei Lembing, Malaya".

ROYAL SOCIETY OF ARTS, COMMONWEALTH SECTION (at John Adam Street, Adelphi, London, W.C.2), at 5.15 p.m.—Mr. Wilfred Brining: "Bauxite and its Importance to the Commonwealth" (Henry Morley Lecture).

INSTITUTION OF ELECTRICAL ENGINEERS, UTILIZATION SECTION (at Savoy Place, London, W.C.2), at 5.30 p.m.—Mr. J. A. Broughall: "Electric Traction".

INSTITUT FRANÇAIS DU ROYAUME-UNI (at Queensberry Place, London, S.W.7), at 6.15 p.m.—Dr. Tomatis (Paris): "Phonation et Audition".*

Friday, May 26

BRITISH PSYCHOLOGICAL SOCIETY, OCCUPATIONAL PSYCHOLOGY SECTION (in the Department of Psychology, Birkbeck College, Malet Street, London, W.C.1), at 1 p.m.—Mr. Denis McMahon: "An International Study of Military Training".

SCIENTIFIC PUBLICATIONS COUNCIL (at the Ciba Foundation, 41 Portland Place, London, W.1), at 6 p.m.—Discussion Meeting on "Time-Lag in the Publication of Scientific Manuscripts".

APPOINTMENTS VACANT

APPLICATIONS are invited for the following appointments on or before the dates mentioned:

LECTURER or ASSISTANT LECTURER IN BACTERIOLOGY—The Registrar, The University, Leeds 2 (May 27).

LECTURER (with an honours degree) IN PHYSICS—The Clerk to the Governors, Woolwich Polytechnic, London, S.E.18 (May 27).

RESEARCH ASSISTANT (with a good degree in chemistry or biochemistry and preferably some research or industrial experience in the lipid field) IN LIPID CHEMISTRY—The Registrar, Brunel College of Technology, Woodlands Avenue, Acton, London, W.3 (May 27).

DEMONSTRATOR (ASSISTANT LECTURER) IN PHYSIOLOGY—The Registrar, The University, Leeds 2 (May 29).

LECTURER IN MATHEMATICS—The Principal, Borough Road College, Isleworth, Middlesex (May 29).

ASSISTANT LECTURER IN PHYSICS—The Registrar, King's College (University of London), Strand, London, W.C.2 (May 31).

LECTURER (graduate with medical qualifications) IN ANATOMY—The Registrar, King's College (University of London), Strand, London, W.C.2 (May 31).

LECTURER (with special interests in physical or inorganic chemistry) IN THE DEPARTMENT OF CHEMISTRY—The Secretary, The University, Edinburgh (May 31).

SENIOR LECTURER/LECTURER IN GEOGRAPHY at the University of New England, New South Wales, Australia—The Secretary, Association of Universities of the British Commonwealth, 36 Gordon Square, London, W.C.1 (Australia and London, May 31).

READER IN MATHEMATICS at Westfield College—The Academic Registrar, University of London, Senate House, London, W.C.1 (June 8).

LECTURER or ASSISTANT LECTURER (medically qualified or otherwise) IN THE DEPARTMENT OF PHYSIOLOGY—The Registrar, University College of South Wales and Monmouthshire, Cathays Park, Cardiff (June 19).

CHAIR OF GEOGRAPHY at University College, Ibadan, Nigeria—The Secretary, Inter-University Council for Higher Education Overseas, 29 Woburn Square, London, W.C.1 (June 20).

LECTURER (preferably with a special interest in either vertebrate zoology or genetics) IN THE DEPARTMENT OF ZOOLOGY, University College, Ibadan, Nigeria—The Secretary, Inter-University Council for Higher Education Overseas, 29 Woburn Square, London, W.C.1 (June 20).

ASSISTANT UNDER-LIBRARIAN (graduate in science or with experience of library administration)—The Librarian, University Library, Cambridge (June 22).

ASSISTANT PROFESSOR (POULTRY GENETICS) (with a Ph.D. or equivalent in genetics, and preferably training in biochemical genetics) IN THE DEPARTMENT OF ANIMAL SCIENCE—Head, Department of Animal Science, University of Alberta, Edmonton, Alberta, Canada (June 30).

CHAIR OF EDUCATION in the University of Hong Kong—The Secretary, Association of Universities of the British Commonwealth, 36 Gordon Square, London, W.C.1 (Hong Kong and London, June 30).

READER IN FUEL SCIENCE in the Newcastle Division of the University—The Registrar, University Office, 46 North Bailey, Durham (June 30).

RESEARCH FELLOW (ORGANIC CHEMIST) IN THE DEPARTMENT OF MEDICAL CHEMISTRY, John Curtin School of Medical Research, Australian National University, Canberra, to work with Prof. Adrien Albert or Dr. D. J. Brown on problems in the pyrimidines, pteridines or other hetero-aromatic series—The Secretary, Association of Universities of the British Commonwealth, 36 Gordon Square, London, W.C.1 (Australia and London, June 30).

RESEARCH FELLOW (with a Ph.D. degree) and a RESEARCH STUDENT (with an M.Sc. or an honours degree) IN THE DEPARTMENT OF PHYSICS, to participate in the research of a small group working on problems of brittle fracture and on the influence of absorbed substances on the strength of solids such as silica and tungsten carbide—Prof. F. R. N. Nabarro, c/o The Registrar, University of the Witwatersrand, Milner Park, Johannesburg, South Africa (June 30).

SENIOR LECTURER or LECTURER IN PHYSICS at the University of Canterbury, Christchurch, New Zealand—The Secretary, Association of Universities of the British Commonwealth, 36 Gordon Square, London, W.C.1 (New Zealand and London, July 31).

SENIOR LECTURERS and LECTURERS (with qualifications in either pure or applied mathematics) IN MATHEMATICS at the University of Canterbury, Christchurch, New Zealand—The Secretary, Association of Universities of the British Commonwealth, 36 Gordon Square, London, W.C.1 (New Zealand and London, August 9).

ASSISTANT LECTURER IN ORGANIC CHEMISTRY—The Registrar, The University, Manchester 13.

ASSISTANT PROFESSOR (Ph.D. or M.B.) IN PHARMACOLOGY—Prof. M. F. Murnaghan, University of Ottawa, Ottawa, Ontario, Canada.

BIOCHEMIST, to supervise all chemical procedures and to conduct research in fields related to blood transfusion in consultation with the Director—The Director, Red Cross Blood Transfusion Service, 409 Adelaide Street, Brisbane, Queensland, Australia.

CHEMIST or BIOCHEMIST (with an honours degree, a good knowledge of general chemistry and an interest in protein chemistry) to investigate the constituents of animal connective tissue together with related enzyme systems—The Director, Low Temperature Research Station, Downing Street, Cambridge.

CHIEF LABORATORY TECHNICIAN (with the City and Guilds Final Certificate in Laboratory Technology (or accepted equivalent) and previous experience in physiology, pharmacology or biochemistry, including the care and maintenance of equipment and apparatus) IN THE DEPARTMENT OF PHYSIOLOGY AND PHARMACOLOGY—Head of the Department of Physiology and Pharmacology, Chelsea College of Science and Technology, Manresa Road, London, S.W.3.

CURATOR (preferably with experience in museum administration, as well as general scientific knowledge, especially in biological fields) of the Coryndon Museum, Nairobi, Kenya—The Secretary, Coryndon Museum, P.O. Box 658, Nairobi, Kenya, East Africa.

JUNIOR BIOCHEMIST, Basic grade (with an appropriate science degree or associateship of the Royal Institute of Chemistry) IN THE CHEMICAL PATHOLOGY LABORATORY, Nottingham General Hospital—The Group Secretary, Nottingham No. 1 Hospital Management Committee, General Hospital, Nottingham.

MASTER TO TEACH MATHEMATICS throughout the school—The Headmaster, Malvern College, Malvern, Worcs.

RESEARCH STUDENTS and ASSISTANTS IN THE DEPARTMENT OF PHYSICS—Prof. D. J. E. Ingram, Department of Physics, University College of North Staffordshire, Keele, Staffs.

SENIOR MATHEMATICS MASTER—The Headmaster, Adams' Grammar School, Newport, Salop.

TECHNICAL RESEARCH ASSISTANT IN THE BOTANY DEPARTMENT, to work with Prof. Street on the establishment of free cell cultures from higher plants—The Registrar, University College of Swansea, Swansea.

REPORTS and other PUBLICATIONS

(not included in the monthly Books Supplement)

Great Britain and Ireland

The Iron and Steel Institute. Notes for Authors. Pp. 16. (London: The Iron and Steel Institute, 1961.) [202

Association of Universities of the British Commonwealth. Report of 1960 Home Universities Conference. First Session: The Future of the General Degree. Second Session: New Universities. Pp. 90.

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London School of Hygiene and Tropical Medicine (University of London), incorporating the Ross Institute. Report on the work of the School for the year 1959–1960. Pp. 151. (London: London School of Hygiene and Tropical Medicine, 1961.) [232

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The Year Book of the Royal Society of London, 1961. Pp. 302. (No. 65.) (London: The Royal Society, 1961.) 21s. [232

National Parks and Access to the Countryside Act, 1949. Eleventh Report of the National Parks Commission for the year ended September 30, 1960. Pp. vi + 71 + 8 plates. (London: H.M. Stationery Office, 1961.) 6s. net. [232

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British Association for Commercial and Industrial Education. A Guide to the Use of the Telephone in Business. Fourth edition. Pp. 20. 3s. 6d. A Guide to the Use of Visual Aids. By L. S. Powell. Pp. 48. 4s. 6d. Report Writing. Second edition. Pp. 23. 4s. (London: British Association for Commercial and Industrial Education, 1961.) [272

Caroline Haslett Memorial Trust. Women Engineers in the U.S.S.R.: a Study of the Education, Employment and Prospects of Women Engineers in the U.S.S.R., carried out under the auspices of the Caroline Haslett Memorial Trust. By L. S. Souter and R. Winslade. Pp. 28. (London: The Caroline Haslett Memorial Trust, 25 Foubert's Place, W.1.) [272

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British Hat and Allied Feltmakers Research Association. Thirteenth Annual Report of the Director of Research for the year ended August, 1960. Pp. 20. (Droylsden, Manchester: British Hat and Allied Feltmakers Research Association, 1961.) [33

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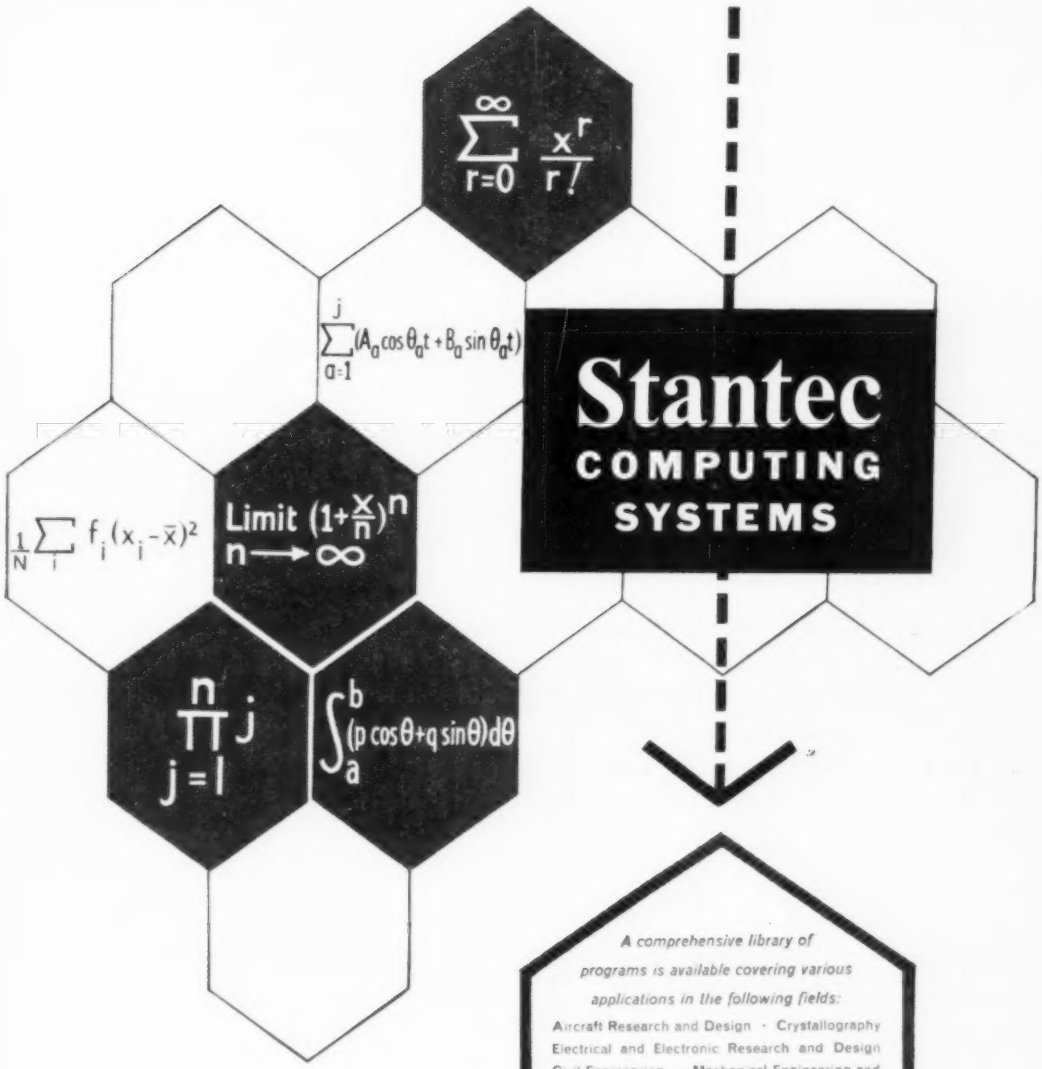

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Further particulars should be obtained from the Secretary, Association of Universities of the British Commonwealth, 36 Gordon Square, London, W.C.1. Applications close, in Australia and London, on August 15, 1961.

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Further particulars should be obtained from the Secretary, Association of Universities of the British Commonwealth, 36 Gordon Square, London, W.C.1. Applications close, in Australia and London, on June 30, 1961.

APPLICATIONS ARE INVITED FOR THE post of Curator of the Coryndon Museum, Nairobi, Kenya. The appointment will be for a period of three years, in the first instance, commencing on July 1, 1961, or as soon after as possible. Candidates should, if possible, have experience in Museum administration as well as general scientific knowledge, especially in biological fields. The post is principally administrative, but will not entail protracted or frequent absence from the Museum buildings. Salary will be in the scale of £2,000 by £60 to £2,540, the point of entry being decided on the basis of previous experience and qualifications. An overseas appointee will receive economy class air passage for himself and wife on taking up the appointment and return passages at the end of three years.—Write in the first instance to: The Secretary, Coryndon Museum, P.O. Box 658, Nairobi, Kenya, East Africa, when further details will be supplied if required.

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Mr. E. J. Drake, Chief Scientific Liaison Officer, Australian Scientific Liaison Office, Africa House, Kingsway, London, W.C.2,

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The newly formed Organisation is an autonomous body financed jointly by the New Zealand Wool Board and Government, and will have an annual income of £100,000. New laboratories are to be built adjacent to a university institution, Canterbury Agricultural College, Lincoln, near Christchurch.

The Director will be expected to plan and organise research into the physical, chemical and biological properties of wool and into other matters related to wool. He will be responsible to the Executive committee, and will be required to develop the Organisation from the initial planning of the laboratories, to the selection of staff, preparation of programmes of research, and dissemination of research findings.

Applicants should have a University degree in science or agriculture, and be experienced in organising and directing research preferably, although not necessarily, in wool science. Applications will be treated in strict confidence and should provide details of age, marital status, nationality, degrees held, names of referees, and full particulars of post graduate experience, and publications. Applications should be addressed to:

The Chairman,
Wool Research Organisation of N.Z. (Inc.).
Box 5115, Wellington, New Zealand.

Further particulars are available from the above, or either the Scientific Adviser, International Wool Secretariat, 18/20 Regent Street, London S.W.1, or the Director, Department of Science and Technology, The Wool Bureau Inc., 360 Lexington Avenue, New York 17, N.Y., U.S.A.

Applications close 31 July 1961

MSL *have been retained to advise on this appointment.*

SENIOR PRODUCTIVITY CONSULTANT

for a company controlling its expanding production by advanced methods of efficient operation.

In a factory using highly instrumented mass production methods, he will advise the General Manager on the application of operational research, production control, method study, work study, systems, procedures, wage incentives and organisation and methods.

Candidates must already hold a similar appointment in private or public industry or be practising industrial consultants. A degree in engineering, science, mathematics or statistical economics is essential. Salary not less than £2,250 with contributory pension scheme and insurance cover. Age 35 to 45. Assistance with house purchase. Please send brief details in confidence quoting reference U.9017 to P. A. Ashworth.

In no circumstances will a candidate's identity be disclosed to our client unless he gives permission after a confidential interview at which he will be given full details of the appointment.

MANAGEMENT SELECTION LIMITED
17 Stratton Street, London, W.1

UNIVERSITY OF NEW ENGLAND
NEW SOUTH WALES, AUSTRALIA
SENIOR LECTURER/LECTURER IN GEOGRAPHY

Applications are invited from honours graduates in geography for the above position. Duties will include work with internal and external students. Applicants should have special qualifications in climatology, as the appointee will be responsible for all undergraduate and postgraduate work in this specialism. Commencing salary will be fixed according to qualifications and experience within the range: Lecturers, £A.1,730 by £A.105 to £A.2,435, Senior Lecturers, £A.2,550 by £A.95 to £A.3,000, plus cost of living allowance. Applicants for the lectureship must state whether they seek a permanent or short-term appointment. A short-term appointment is available only to applicants who are normally resident outside Australia. The salary will be determined according to qualifications and experience and will be payable from the date of embarkation by the shortest route for Armidale. Provision is made for travel and removal expenses and in the case of a permanent appointment for superannuation and assistance in buying or building a house.

Further information may be obtained from the Secretary, Association of Universities of the British Commonwealth, 36 Gordon Square, London, W.C.1. Applications close, in Australia and London, on May 31, 1961.

EXPERIMENTAL OFFICER OR ASSISTANT Experimental Officer required by Royal Military College of Science, Shrivenham, Berkshire. To assist with laboratory classes at University level, and research. Extensive well-equipped laboratories. Should have specialist knowledge of techniques for measurement of thermal conductivity and related properties in metals especially anisotropic materials. Qualified man encouraged to do personal research for higher degrees. Qualifications: G.C.E. (A level), Pass degree, H.N.C. or equivalent. Age: Assistant Experimental Officer, 18 to 28, Experimental Officer, minimum 27. Salary: Assistant Experimental Officer, £443 to £957, Experimental Officer, £1,057 to £1,296. Starting salary allows credit for approved post-graduate experience and National Service. Opportunity for establishment and promotion. Quarters for single man, possibility of house for married man.—Forms from Ministry of Labour, Technical and Scientific Register (K), 26 King Street, London, S.W.1, quoting reference A.198/1A.

LABORATORY ANIMALS CENTRE, MEDICAL Research Council Laboratories, Woodmansterne Road, Carshalton, Surrey, require an experienced Senior Laboratory Technician in their Bacteriological Laboratory. Salary in accordance with age and experience, plus London weighting.—Apply the Director.

THE PATENT OFFICE
OFFERS SCIENTISTS A CAREER WITH AN ASSURED FUTURE

SALARY. Starting salary within the scale £793 to £1,719 according to experience, with advances in the scale to £941 after two years and to £1,324 after 3 to 5 years, for those starting below these points. One promotion only (prospects excellent) raises maximum to £2,715. Further prospects up to £4,415.

QUALIFICATIONS. Age 21 to 35 and Degree or Diploma of Technology with first- or second-class honours in physics, chemistry, engineering or mathematics, or equivalent professional qualification, e.g., A.Inst.P., A.R.I.C., or corporate membership of I.C.E., I.Mech.E. or I.E.E.

INTEREST. The examination of patent specifications will maintain your knowledge of science and technology completely up-to-date and will give you inside knowledge of new manufactures well ahead of the public at large.

CONDITIONS. Location, London. Five-day week. Annual leave 4½ rising to 6 weeks with considerable freedom as to when it is utilized. Posts are permanent and pensionable (non-contributory).

Write or telephone for further information or for a visit to see the work. *The Superintending Examiner (B. Staff), The Patent Office, 25 Southampton Buildings, London, W.C.2. Holborn 8721, Ext. 324.*

THE EXPANDITE GROUP OF COMPANIES require qualified physicists, physical chemists and theoretical engineers to establish a new Central Research Laboratory for research in the fields of rheology, corrosion prevention, adhesives, structural joint movement stresses and allied fields. Modern premises will provide first-class facilities including special apparatus where necessary. Good salary and staff pension and life assurance scheme will be available to successful applicants. —Applications in confidence, giving full details, including salary required, to Group Personnel Manager, 1-9 Chase Road, London, N.W.10.

NATIONAL COLLEGE OF RUBBER TECHNOLOGY
HOLLOWAY, LONDON, N.7

The Governors invite immediate applications for the following teaching appointments, which provide opportunities for personal and team research:

(a) LECTURER IN POLYMER CHEMISTRY. Applicants should hold a first- or second-class Honours Degree of a United Kingdom University and have a special interest in physical chemistry. Experience with polymers desirable, but not essential. Personal research expected for which facilities are available. Salary scale: £1,421 by £35 to £1,561 by £40 to £1,601.

(b) INSTRUCTOR IN POLYMER CHEMISTRY. Applicants should be Graduates or hold the Higher National Certificate in Chemistry. Duties will involve demonstrating and teaching in a laboratory devoted to polymer chemistry. Salary scale: £751 by £27 10s. to £1,163 10s. by £37 10s. to £1,201, plus allowance for degree, etc. Commencing salary according to qualifications and experience.

(c) LECTURER IN POLYMER CHEMISTRY. Applicants should hold a degree or equivalent technological qualification and have had works experience in the technology of plastics and rubbers. Salary scale: £1,421 by £35 to £1,561 by £40 to £1,601.

(d) INSTRUCTOR IN LIGHT ENGINEERING. Applicants should be trained demonstrators of light machine tools, with knowledge of instruments, preferably as used in rubber and plastics industry. Salary scale: £751 by £27 10s. to £1,163 10s. by £37 10s. to £1,201 plus allowance for degree, etc. Commencing salary according to qualifications and experience.

(e) SENIOR LECTURER IN ENGINEERING. Applicants should be qualified engineers with personality and experience to introduce an engineering bias and ability to plan courses and organize equipment for new laboratories. Salary scale: £1,601 by £50 to £1,801.

Apply, stating post in which interested, for application form and further particulars.

R. H. CURRELL, F.C.A.
Clerk.

MIDDLESEX COUNTY COUNCIL EDUCATION COMMITTEE
ACTON TECHNICAL COLLEGE
HIGH STREET, ACTON, W.3

Principal: W. F. Giddings, B.Sc.(Eng.), A.C.G.I., D.I.C., M.I.E.E.

Applications are invited for the following post, duties to commence September 1, 1961:

Assistant Grade B, to teach Chemistry for Ordinary National Certificate and General Certificate of Education Advanced Level courses. Candidates should possess a degree or graduate equivalent. Some teaching experience is desirable.

Salary: £738 to £1,201 per annum. Additions may be given for industrial experience (up to £330 above the minimum), training and study (up to £120 above the maximum), qualifications (£165 above the maximum).

Forms of application and further particulars may be obtained from the Principal (foolscap s.a.e.) to whom the completed forms should be returned within fourteen days of the appearance of this advertisement.

C. E. GURR, M.Sc., Ph.D.,
Chief Education Officer.

UNIVERSITY OF ST. ANDREWS
RESEARCH ASSISTANT IN CRYOGENICS (LIQUID He^3)

Applications are invited for a Research Assistantship in very low temperature physics in the Department of Natural Philosophy, St. Salvator's College, to assist in the design and construction of liquid He^3 cryostats and refrigeration cycles. Experience in the handling of liquid He^4 is essential, and of He^3 of advantage but not essential. The post is part of a D.S.I.R. Research Project. Salary £1,000 per annum for three years; for a suitably experienced person the salary may be higher for a shorter period. F.S.S.U. benefits if successful applicant is already within that scheme, but not otherwise.

Applications, with names of two referees, should be lodged with the Joint Clerk to the University Court, College Gate, St. Andrews, not later than June 15, 1961.

COLLEGE OF ENGINEERING AND TECHNOLOGY OF THE UNIVERSITY OF DELHI

Applications are invited for the positions of Professors to advise on the development of the following Departments of the new College of Engineering and Technology of the University of Delhi:

1. **Mechanical Engineering (Thermodynamics)**
2. **Mechanical Engineering (Applied Mechanics)**
3. **Metallurgy**

This new College is being established by the Government of India. British Industry has agreed to assist the College by the provision of teaching and research equipment, and the U.K. Government has agreed to provide certain British members of the Professorial staff during the initial 5 years. These appointments will be made by the Secretary of State for Commonwealth Relations and all personal emoluments will be paid by the United Kingdom Government. Applications will be considered by a Technical Committee composed of representatives from the Professional Engineering Institutions, the Commonwealth Relations Office and the Federation of British Industries.

Applicants should have appropriate academic and professional qualifications, teaching and research experience. Duties will include advising on the development of undergraduate and postgraduate studies and on the planning of equipment; and teaching in undergraduate and postgraduate courses and taking part in and developing research. Professors will qualify for D.S.I.R. research grants as if they were resident in the United Kingdom.

The appointments are intended to be for a 5-year period, although shorter terms of from 2 years would be considered. It may be possible to arrange for an applicant to be seconded from his present appointment.

RATES OF PAY AND CONDITIONS

Remuneration will consist of basic salary (subject to U.K. tax) plus overseas allowance (non-taxable). Children's allowance, medical benefits up to National Health Scheme scale, free passages for applicant's family and free furnished accommodation will be provided. No Indian Income Tax is payable.

Salary within the range of £2,600–£3,600 a year according to the applicant's qualifications and experience. Overseas Allowance £1,670 a year (married) (plus children's untaxed allowances—particulars on application); £1,080 a year (single).

First-class return passages between India and the United Kingdom are provided after two academic years' service. Privilege leave is granted at the rate of one calendar week for each two calendar months' service in India and may be accumulated until such time as the selected officers visit the U.K.

U.K. Superannuation position will be preserved during tour of duty.

Write for application form to:
SECRETARY OF STATE FOR
COMMONWEALTH RELATIONS
TECHNICAL ASSISTANCE DEPARTMENT,
DOWNING STREET,
LONDON, S.W.1.

A.P.C.
SENIOR HEALTH PHYSICIST

Applications are invited for the post of Senior Site Health Physicist, to be responsible initially for Radiological Safety during commissioning of the Nuclear Power Station at Trawsfynydd in North Wales.

Candidates should be between 28 and 35 years of age and should have a good degree in an appropriate subject. Several years practical experience in Radiological Safety is essential.

The successful candidate will be expected to take up residence near Trawsfynydd for an extended period during commissioning, and to devote the intervening periods between commissioning assignments to assessment of the radiological safety problems of subsequent designs as a member of the Radiological Safety Group at the Head Office of the Company in London.

The post is a permanent one, with contributory superannuation scheme; salary will be in accordance with age, qualifications and experience and generous allowances will be made on transfer to Site.

Applications, giving full details of age, qualifications and experience, should be sent to:

The Personnel Manager (Ref. N/181),
Atomic Power Constructions Limited,
P.O. Box 90,
28 Theobalds Road,
London, W.C.1.

UNIVERSITY OF ST. ANDREWS

Applications are invited for the post of Research Assistant in a Human Cytogenetics Laboratory shortly to be opened within the University Department of Pathology, Queen's College, Dundee. The appointment will be initially for a period of up to three years, and would be suitable for a graduate in science (possibly in zoology). Salary £650 annual increments £50 subject to maximum salary, if appointment continued, of £950.

Applicants should provide the names of two referees, with details of previous appointments and scientific work. Applications should be sent, before June 1, 1961, to: Patrick Cumming, Joint Clerk to the University Court, Queen's College, Dundee.

METAL SURFACES RESEARCH

John Lysaght (Australia) Limited are seeking a Research man with prior experience to investigate metal surface phenomena related mainly to low carbon and silicon steel sheet and strip and galvanized iron. The initial approach will be fundamental but with a view to possible practical application in the fields of coatings, surface properties or reactions. It is hoped that duties will include supervision of a small group on corrosion research.

The Company produces about 700,000 tons of sheets per annum, and has an air-conditioned, well equipped Central Research Laboratory with a staff of 20, and excellent Works Laboratories with a staff of over 100. Publication of results is encouraged.

The appointment would be in the first place for three years to Lysaghts Central Research Laboratory at Newcastle Works. Travelling expenses would be paid, and a salary in the range £A 1,800 to £A 2,500 depending on experience and qualifications. Staff arrangements, superannuation, leave, etc., are good.

If you are interested, please apply in writing to The Research Superintendent, John Lysaght (Services) Limited, G.K.N. House, 22 Kingsway, London, W.C.2, before June 12 who will treat any application as confidential and provide any additional information.

WEST OF SCOTLAND AGRICULTURAL COLLEGE

Applications are invited for a post of Assistant in Bacteriology or dairying, but exceptionally from those possessing a suitable Diploma in Dairying. The salary will depend on age, qualifications and experience, and will be on one or other of the following scales: Grade III (National), £1,004 rising to £1,570; Grade IV (National), £718 (honours graduates £738) rising to £993. Grade B (National), £582 (age 21) rising to £978.

Conditions of appointment and application forms may be obtained from the Secretary, 6 Blythswood Square, Glasgow, C.2, with whom applications should be lodged not later than June 10, 1961.

THE TOBACCO MANUFACTURERS' Standing Committee invites applications for the post of Laboratory Animals' Superintendent for the Committee's Research Unit which is being built at Harrogate, Yorkshire. The Research Unit will provide facilities for a combined programme of chemical research and bioassay, the animal unit will be of intermediate size, and the Superintendent will eventually be responsible for a large colony of animals. Candidates will have to provide evidence of above average ability and practical experience in running an animal unit. A salary commensurate with the responsibility involved will be paid. The appointment is permanent and pensionable and assistance will be given with housing.—Applications in the first instance to the Secretary, 6-10 Bruton Street, London, W.1.

CORROSION RESEARCH

John Lysaght (Australia) Limited are seeking a Research man with experience and special training in corrosion. An immediate objective will be to extend existing knowledge of the under-water corrosion of zinc and galvanized iron, in terms of fundamental electrochemistry, and methods of protection, and to investigate the effects of aluminium and other elements in the zinc on atmospheric and under-water corrosion.

The corrosion research will be part of a general approach to reactions at metal surfaces, extending a programme which has been in operation for some time.

The Company produces about 700,000 tons of sheets per annum, and has an air-conditioned, well equipped Central Research Laboratory with a staff of 20, and excellent Works Laboratories with a staff of over 100. Publications of results is encouraged.

The appointment would be in the first place for three years to Lysaght's Central Research Laboratory at Newcastle Works. Travelling expenses would be paid, and a salary in the range £A.1,500 to £A.2,200 according to experience and qualifications. Staff arrangements, superannuation, leave, etc., are good.

If you are interested, please apply in writing to The Research Superintendent, John Lysaght (Services) Limited, G.K.N. House, 22 Kingsway, London, W.C.2, before June 14, who will treat any application as confidential and provide any additional information.

UNIVERSITY OF MANCHESTER

Applications are invited for the post of Research Fellow in Chemical Crystallography in the Department of Chemistry in the Faculty of Science to undertake investigations into the structures of complex natural products of biological importance and novel structural interest. Excellent facilities are available for single crystal analysis and electronic computation. The Fellowship, valued at £875 per annum, will be available for one year from October 1, 1961, in the first instance, but renewal may be possible. Applicants should have had training in single crystal analysis and should possess a Ph.D. degree or have had at least three years' postgraduate experience.

Applications should be received not later than May 31, 1961, by the Registrar, University of Manchester, Manchester, 13, from whom further particulars and forms of application may be obtained.

AUSTRALIA

UNIVERSITY OF NEW SOUTH WALES

The University wishes to appoint Senior Lecturers and Lecturers in the following Faculty:

FACULTY OF SCIENCE

Applied psychology (psychometrics and experimental psychology). Botany. Mathematics. Physics.

Salary: Senior Lecturer, £A.2,586 range £A.3,036 per annum; Lecturer, £A.1,766 range £A.2,471 per annum. Commencing salary is determined by qualifications and experience. Subject to passing medical examination appointees will be eligible to contribute to the State Superannuation Fund. First-class ship fares to Sydney of appointees and family will be paid.

Four copies of applications, including the names of two referees, should be lodged with the Agent-General for New South Wales, 56-57 Strand, London, W.C.2, England, and a copy forwarded to the Appointments Section, The University of New South Wales, Box 1, Post Office, Kensington, N.S.W., Marked SA1.

BIOCHEMIST (BASIC GRADE). CANDIdates should hold a degree (preferably with honours) in chemistry or biochemistry, or an equivalent qualification. The person appointed will work in the University Department of Pathological Biochemistry under direction of the Consultant Biochemist. He will require to share in the routine work of the Department but there will also be opportunity for conducting original work. Salary according to Whitley scale commencing at £730 per annum (first- or second-class honours graduates).—Application should be made within fourteen days to the Consultant Biochemist, the Royal Infirmary, Glasgow, C.4 (from whom further information may be obtained), and should give the names of two referees.

CAMBERWELL HOSPITALS MANAGEMENT COMMITTEE

The Biochemistry laboratory at Dulwich Hospital requires a Technician or Junior Technician who wishes to take the Final I.M.L.T. examination in Biochemistry. A suitable candidate would be considered for promotion to Senior I Technician if successful in the Final examination. The laboratory has been reorganized and is expanding to undertake all the biochemical investigations for the Camberwell Group. Experience would be obtained in modern techniques for all types of routine investigations including electrophoresis, serum enzyme investigations, etc.

Applications to Consultant Pathologist, Dulwich Hospital, East Dulwich Grove, London, S.E.22.

THE DISTILLERS COMPANY LIMITED

DEVELOPMENT CHEMIST

The Chemical Division of the Company wish to appoint a Chemist at their Carbon Dioxide Development Department at Dagenham.

The work will involve investigations intended to improve and develop production technique, and to extend the use and applications of carbon dioxide in industry.

Candidates, aged not over 30, should possess a degree in chemistry or an equivalent qualification, and experience in pilot plant operation, laboratory control or chemical production would be an advantage.

Write:
STAFF MANAGER
THE DISTILLERS COMPANY LIMITED
21/22 BOLTON STREET
LONDON, W.1.

Quote Ref. 30/61.N.

UNIVERSITY OF LEEDS

DEPARTMENT OF PHYSIOLOGY

Applications are invited for appointment as Demonstrator (Assistant Lecturer) in Physiology at a salary on the scale £1,050 by £50 to £1,150 a year if medically qualified, or within the range £800 to £950 a year if not medically qualified.

Applications (three copies), stating date of birth, qualifications and experience, together with the names of three referees, should reach the Registrar, the University, Leeds, 2 (from whom further particulars may be obtained) not later than May 29, 1961.

UNIVERSITY OF BRITISH COLUMBIA

BIOPHYSICIST

METEOROLOGIST

The Physics Department invites inquiries for vacancies at the Assistant Professor rank in (a) Biophysics and (b) Meteorology. In each case the position involves both teaching and research and the potential in these areas will be given greater weight than experience. The appointee will be given an opportunity to initiate his own programme of course work and research. The minimum salary for an Assistant Professor is $7,000. The appointment is required for the Session commencing in September.

Those interested should address their inquiries to: G. M. Shrum, Physics Department, University of British Columbia, Vancouver 8, B.C.

MARINE BIOLOGY STATION

UNIVERSITY COLLEGE OF NORTH WALES

Applications are invited for the post of Lecturer or Assistant Lecturer in Marine Zoology at the Marine Biology Station, University College of North Wales. Preference will be given to candidates qualified to carry out research in Electrophysiology. The salary scale for a Lecturer is £1,050 by £50 to £1,400 by £75 to £1,850, and for an Assistant Lecturer it is £800 by £50 to £950 per annum. In addition there are F.S.S.U. benefits and family allowances. The appointment will date from October 1, 1961.

Two copies of the application should reach the Registrar, University College of North Wales, Bangor, from whom further particulars may be obtained, not later than June 6, 1961.

CENTRAL ELECTRICITY BOARD

SOUTH EASTERN REGION
NORTH THAMES DIVISION

Applications are invited for the following appointment:

REACTOR PHYSICIST

BRADWELL (NUCLEAR) GENERATING STATION (ESSEX)

Salary range £1,920 to £2,085 per annum. The successful applicant will be responsible to the Station Superintendent for the overall reactor performance assessment, for fuel and absorber programmes, and for technical advice on all matters relating to the safe and efficient operation of the reactors.

Applicants should possess a good Honours Degree in Physics, Engineering or Mathematics, and should have held a responsible position in Industry. Experience in the design or operation of nuclear reactors is essential.

Training will be given to the successful applicant before taking up the appointment.

Applications, quoting Reference S.V. No. 1499, stating age, qualifications, experience and present position, should be sent to the Central Electricity Generating Board, South Eastern Region, North Thames Division, West Farm Place, Chalk Lane, Cockfosters, Barnet, Herts, to arrive not later than June 3, 1961.

UNIVERSITY OF CANTERBURY

CHRISTCHURCH, NEW ZEALAND
SENIOR LECTURERS AND LECTURERS IN MATHEMATICS

Applications are invited for the above-mentioned posts. Qualifications in either pure or applied mathematics will be acceptable and appointees will be expected to engage in research in their own fields or to assist with work in the field of rocket ballistics already in progress in the Mathematics Department. The Department is equipped with an I.B.M. 1620 Computer which may be employed to assist with research. The salary for a Lecturer will be at the rate of £1,250 rising by annual increments of £75 to £1,700 per annum and for a Senior Lecturer at the rate of £1,750 by annual increments to £2,000 per annum. Commencing salary in accordance with qualifications and experience. Approved fares to Christchurch will be allowed for an appointee, his wife and children. In addition actual removal expenses will be allowed within certain limits.

Further particulars and information as to the method of application may be obtained from the Secretary, Association of Universities of the British Commonwealth, 36 Gordon Square, London, W.C.1. Applications close, in New Zealand and London, on August 9, 1961.

GOVERNMENT OF NORTHERN IRELAND

PRINCIPAL SCIENTIFIC OFFICER/SENIOR SCIENTIFIC OFFICER

Applications invited for pensionable post in Crop and Animal Husbandry Division of Ministry of Agriculture. Qualifications: Degree in agriculture, sound practical knowledge of crop and animal husbandry and extensive postgraduate experience in research or advisory work. Preference for ex-Service candidates. Grading and starting pay offered to the successful candidate will depend on his qualifications and experience. Salary scales: Principal Scientific Officer, £1,716 to £2,418; Senior Scientific Officer, £1,342 to £1,654. In addition to research work, teaching duties may have to be undertaken in the Faculty of Agriculture, Queen's University, Belfast.

Application forms obtainable from Secretary, Civil Service Commission, Stormont, Belfast 4, must be returned by June 1, 1961.

FULMER RESEARCH INSTITUTE LTD.

STOKE POGES, BUCKINGHAMSHIRE

Physical Chemists required for experimental work on a wide range of problems in the fields of thermochemistry, chemical thermodynamics, and inorganic chemistry. A competitive salary between approximately £800 and £1,500, in accordance with qualifications and experience will be paid. One post offers an excellent opportunity to a young graduate without experience wishing to obtain a training in advanced research methods.

Applications should be addressed to the Director of Research.

FEDERAL GOVERNMENT OF NIGERIA

SPECIALIST OFFICER (ENTOMOLOGIST)

REQUIRED by the Federal Department of Agricultural Research, Ibadan, to be employed on studies of insect pests of plants and plant products, and to devise practical control methods, with special reference to yam beetle investigations.

Candidates must possess a university first- or second-class honours degree in natural science (zoology or entomology) plus two years' postgraduate experience or training. Only candidates between the ages of 22 and 30 years will be considered.

Appointment on contract for two tours of 18-24 months in the first instance with prospect of extension. Salary according to qualifications and experience in the scale £1,434 to £2,196 per annum (including inducement addition), plus gratuity of £150 on satisfactory completion of service. Outfit allowance of £60 on salaries under £1,741. Free passages for officer and wife. Children's allowances while separated. Liberal home leave on full pay. Income tax at low local rate. Quarters at low rent.

Write for application forms and further particulars, stating briefly age, qualifications and experience, to the Recruitment Attaché, Office of the High Commissioner for Nigeria, Nigeria House, 9 Northumberland Avenue, London, W.C.2, quoting B17/2.

UNIVERSITY OF SOUTHAMPTON

HAWKER-SIDDELEY READERSHIP AND LECTURESHIP IN NOISE RESEARCH

Applications are invited for the permanent University posts of Reader and Lecturer in Noise Research tenable in the Department of Aeronautics and Astronautics at the University of Southampton. Candidates for the Readership should have experience in acoustics, stochastic processes, or aerodynamics and should be able to lead research in one of these fields. The successful candidate will be expected to lecture to postgraduate students. Candidates for the post of Lecturer should have a good honours degree or its equivalent, together with some research experience, in one of these subjects. Applicants need not necessarily have had aeronautical experience. The salary for the Readership will be on the scale of £1,650 by £75 to £2,400 by £25 to £2,425, and for the Lectureship on the scale of £1,050 by £50 to £1,400 by £75 to £1,850, with a merit bar at £1,475. F.S.S.U. and child allowances.

Further particulars of either post may be obtained from the Secretary and Registrar, The University, Southampton, to whom applications (seven copies from U.K. applicants) should be sent before June 24, 1961.

INSTITUTE OF CANCER RESEARCH, Royal Cancer Hospital. An opportunity exists in the Physics Department, Sutton, Surrey, for a Biochemist to join a team engaged in studies of the Biochemistry of bone using radioactive tracer techniques. Candidates should possess a first- or second-class honours degree in biochemistry or chemistry, and the possession of a higher degree would be an advantage, but is not essential. Salary on M.R.C. scales in the range £850 to £1,250.—Applications, with names of two referees, to the Secretary, 33 Sumner Place, S.W.7, quoting ref. 300/G/8.

GLASSHOUSE CROPS RESEARCH INSTITUTE. Head of Mycology and Bacteriology Department. Applications invited for this post, which will fall vacant on October 1, 1961, on retirement of present holder. Candidates should have wide experience of research on plant diseases caused by fungi and bacteria; a special interest in microbiological problems, e.g., as associated with soil or mushroom composts, would be an advantage. Appointment in Principal Scientific Officer grade, £1,666 (£1,716 on January 1, 1962) to £2,418.—Further details available from Secretary to the Institute, Worthing Road, Rustington, Littlehampton, Sussex, to whom applications, with names of three referees, should be submitted before June 30, 1961.

UNIVERSITY OF BIRMINGHAM

DEPARTMENT OF CIVIL ENGINEERING

Applications are invited for three Lectureships in Civil Engineering. Salary within the scale £1,050 by £50 to £1,400 by £75 to £1,550; £1,550 by £75 to £1,850, according to qualifications and experience. Appointments will date from October 1, 1961, and carry F.S.S.U. and family allowance benefits. Applicants should have a good honours degree in engineering or applied mechanics and one of the following: (a) Theoretical and experimental experience in strength and elasticity of materials, including experimental stress analysis. (b) Specialized knowledge of modern structural theory and, in particular, of plastic design. (c) Knowledge of reinforced concrete theory and design. The Department is well equipped for Structural and Experimental Stress Analysis research which would be encouraged.

Applications (three copies), naming three referees, should be sent by June 12, 1961, to the Registrar, the University, Edgbaston, Birmingham, 15, from whom further particulars may be obtained.

UNIVERSITY OF LONDON KING'S COLLEGE

The College will require on October 1, 1961, or as soon as possible thereafter, a Lecturer in Electrical Engineering. Applicants should have a good honours degree in electrical engineering. Preference may be given to an applicant with special interests in electrical machinery.

Salary scale: £1,050 by £50 per annum to £1,400 then by £75 per annum to £1,625; then subject to review by £75 to £1,850. A London allowance of £60, family allowances, and F.S.S.U. benefits will also be payable.

Conditions of appointment and application forms may be obtained from the Registrar, King's College London, Strand, W.C.2. Completed forms must reach him by June 7.

DALHOUSIE UNIVERSITY

HALIFAX, NOVA SCOTIA, CANADA

As part of an expansion programme applications are invited for the following positions:

Assistant Professor in Microanatomy to teach medical and science students and conduct research in embryology. Preference will be given to candidates with a science degree in zoology or medical qualification.

Assistant Professor in Gross Anatomy primarily to teach gross anatomy, with opportunities to participate in research and in other responsibilities of the department. Modern facilities for research available. The salary for an Assistant Professor with medical qualifications will be not less than $8,500, depending upon qualification.

Inquiries for both appointments should be addressed to Professor R. L. de C. H. Saunders at Canada House, London, England.

WESTFIELD COLLEGE (UNIVERSITY OF London), Hampstead, N.W.3. Applications are invited from men and women graduates for the post of Assistant Lecturer in Experimental Physics. The successful applicant will be required to collaborate in research in high energy nuclear physics using the accelerators of C.E.R.N. and the Rutherford Laboratory. Salary scale £800 by £50 to £950 per annum, plus London allowance (£60), with benefit of family allowances and superannuation (F.S.S.U.). The appointment will date from October 1, 1961.—Further particulars may be obtained from the Secretary to Council, Westfield College, Hampstead, London, N.W.3, to whom applications (five copies), stating age, qualifications and experience, together with the names of three referees, should be submitted by Friday, June 9.

AN ORGANIC CHEMIST IS REQUIRED to assist in a project of research into the composition of cottonseed oil and the properties of its glycerides. The post offers good opportunities of fundamental research and results of the investigation will be available for publication. The candidate should hold a university degree in chemistry.—Apply in writing to the Director of Research, The British Food Manufacturing Industries Research Association, Randalls Road, Leatherhead, Surrey, giving details of educational qualifications and experience, and state salary expected. The post carries comparable pension and life insurance rights. Applications should be marked "Private and Confidential."

UNIVERSITY OF LONDON KING'S COLLEGE

The College will require on October 1, 1961, an Assistant Lecturer in Physics.

Salary scale: £800 by £50 per annum to £950. A London allowance of £60, family allowances, and F.S.S.U. benefits will also be payable.

Facilities for research in either experimental or theoretical physics will be provided.

Conditions of appointment and application forms may be obtained from the Registrar, King's College, London, Strand, W.C.2; completed forms must reach him by May 31.

WELSH COLLEGE OF ADVANCED TECHNOLOGY

DEPARTMENT OF MATHEMATICS

Applications are invited for the following posts: One Principal Lecturer. One Assistant Lecturer Grade "B." In addition to teaching duties, the Principal Lecturer will be required to assist the Head of the Department in administrative work. Teaching and industrial experience are desirable. The department is equipped with a Stantec Zebra Electronic Computer and is shortly commencing courses for a postgraduate Diploma in Operational Research and Diploma in Technology in Statistics. It is desirable that the Principal Lecturer should have appropriate research interests. Candidates for the Grade "B" post should be honours graduates. A recently qualified graduate would be considered. Salaries: Principal Lecturer, £1,750 by £50 to £1,900. Assistant Lecturer (Grade "B"), £700 by £27 10s. to £1,150 plus allowances (minimum for a good honours graduate £895).

Forms of application and further particulars may be obtained from the Registrar at the College, Cathays Park, Cardiff, to whom completed forms are to be returned by June 3, 1961.

ROBERT E. PRESSWOOD,
Clerk to the Governors.

WELSH COLLEGE OF ADVANCED TECHNOLOGY

DEPARTMENT OF COMMERCE AND ADMINISTRATION

Applications are invited for the post of Reader in the Human Aspects of Management. Duties to begin on September 1, 1961. Salary scale: £1,800 by £50 to £2,100 per annum.

Full particulars and forms of application may be obtained from the Registrar at the College, Cathays Park, Cardiff, to whom completed forms should be returned not later than June 3, 1961.

ROBERT E. PRESSWOOD,
Clerk to the Governors.

THE POLYTECHNIC

309 REGENT STREET, LONDON, W.1

DEPARTMENT OF MATHEMATICS AND PHYSICS

Applications are invited for a full-time post as Lecturer in Physics, duties to commence on September 1, 1961. Candidates should possess a good Honours degree in Physics and be able to lecture on the subject up to B.Sc. (Special) Physics standard. Previous lecturing, industrial or research experience is desirable. Research work is encouraged in the Department. The salary scale commences at £1,370 per annum, rising by annual increments of £35 to £1,550, plus London allowance of £38 or £51 per annum.

A form of application, which should be returned not later than June 3, may be obtained by sending a stamped addressed foolscap envelope to the undersigned.

J. E. RICHARDSON,
Director of Education.

THE AGRICULTURAL RESEARCH COUNcil require for their Weed Research Organization, near Oxford, an Assistant in the Information Section, to commence September 1. Duties include abstracting, indexing, and responsibility for the Organization's Library. A degree and some knowledge of languages are desirable. The appointment would be in the grade of Assistant Experimental Officer (£450 10s. at 18 to £776 at 26 to £983) for graduates, and for non-graduates under 22 having acceptable qualifications.—Applications, with names of two referees, to the Secretary, Agricultural Research Council, Weed Research Organization, Begbroke Hill, Sandy Lane, Kidlington, Oxford, within two weeks.

UNIVERSITY COLLEGE
IBADAN, NIGERIA

Applications are invited for Lectureship in Department of Geography. Preference given to applicants with special qualifications in climatology and hydrology. Appointment to commence October, 1961. Salary scale: £1,200 by £75 to £1,650 (bar); £1,725 by £75 to £2,175 per annum. Passages paid for appointee, wife and up to five children under 11 years, on appointment, annual overseas leave, and termination. F.S.S.U. Children's, car and outfit allowances. Part-furnished accommodation at rent not exceeding 7.7 per cent of salary.

Detailed applications (six copies), naming three referees, by June 18, 1961, to Secretary, Inter-University Council for Higher Education Overseas, 29 Woburn Square, London, W.C.1, from whom further particulars may be obtained.

UNIVERSITY COLLEGE
IBADAN, NIGERIA

Applications are invited for two Lectureships in Department of Physics. Appointments to commence October, 1961. Salary scale: £1,200 by £75 to £1,650 (bar); £1,725 by £75 to £2,175 per annum. Passages paid for appointee, wife and up to five children under 11 years, on appointment, annual overseas leave and termination. F.S.S.U. Children's, car and outfit allowances. Part-furnished accommodation at rent not exceeding 7.7 per cent of salary.

Detailed applications (six copies), naming three referees, by June 28, 1961, to Secretary, Inter-University Council for Higher Education Overseas, 29 Woburn Square, London, W.C.1, from whom further particulars may be obtained.

UNIVERSITY COLLEGE
IBADAN, NIGERIA

Applications are invited for following vacancies in Department of Chemistry: (a) Lectureship in Physical Chemistry, (b) Micro-Analyst. Appointments to commence October, 1961. Salary scales: (a) £1,200 by £75 to £1,650 (bar); £1,725 by £75 to £2,175 per annum; (b) £1,050 by £25 to £1,100 (bar); £1,150 by £50 to £1,400 per annum. Passages paid for appointee, wife and up to five children under 11 years, on appointment, annual overseas leave and termination. F.S.S.U. or equivalent for Micro-Analyst. Children's, car and outfit allowances. Part-furnished accommodation at rent not exceeding 7.7 per cent of salary.

Detailed applications (six copies), naming three referees, by June 22, 1961, to Secretary, Inter-University Council for Higher Education Overseas, 29 Woburn Square, London, W.C.1, from whom further particulars may be obtained.

UNIVERSITY COLLEGE OF SWANSEA

Applications are invited for a Senior Research Studentship in either Engineering or Chemical Engineering or Metallurgy which is tenable for one year from October 1, 1961, and may be renewed for a second year. The value of the Studentship is between £500 and £700 per annum.

Further particulars may be obtained from the Registrar, University College, Singleton Park, Swansea, by whom applications (four copies) must be received by Saturday, June 10, 1961.

MANCHESTER COLLEGE OF SCIENCE AND TECHNOLOGY
(Faculty of Technology in the University of Manchester)

Applications are invited for a Lectureship in Paper Technology with the title and status of Lecturer in the University of Manchester. Candidates should possess a good honours degree in mathematics, physics or paper technology and be prepared to undertake research work; there will be opportunity to study for a higher degree. Industrial experience would be an advantage. Salary on scale: £1,050 by £50 to £1,400 by £75 to £1,850 per annum. Superannuation under the F.S.S.U. Family allowances.

Conditions of appointment and form of application may be obtained from the Registrar, the Manchester College of Science and Technology, Manchester, 1. The last date for the receipt of applications is Saturday, June 3, 1961.

ASSISTANT LIBRARIAN AND ABSTRACTOR (woman) with knowledge of organic chemistry to B.Sc. standard required in London. Commencing salary £850 per annum with prospects of further increments for suitable applicant.—Please apply by confidential letter, giving qualifications and experience to the Secretary, the British Plastics Federation, 47/48 Piccadilly, London, W.1.

BISRA

HEAT TRANSFER

A graduate is required at the Sheffield Laboratories of the Mechanical Working Division of the British Iron and Steel Research Association. The post in this Division, in which research on metal working process is carried out, would particularly suit a physicist who has an interest in heat transfer problems. A starting salary, depending on age and experience, of up to £1,000 per annum is envisaged and rapid advancement on this can be expected by a man prepared to use initiative and accept responsibility. The post will be superannuated under the F.S.S.U.

Written applications only quoting "M.W.21" to the Personnel Officer, B.I.S.R.A., 11 Park Lane, London, W.1.

UNIVERSITY OF LONDON KING'S COLLEGE

The College will require on October 1, 1961, a Lecturer in Anatomy. Applicants should be graduates with medical qualifications.

Salary on the Junior scale: £950 by £50 to £1,150 per annum, plus a London allowance of £60, family allowances, and F.S.S.U. benefits.

Full conditions of appointment and application forms may be obtained from the Registrar, King's College, London, Strand, W.C.2; completed forms must reach him by May 31.

UNIVERSITY OF BRITISH COLUMBIA
LOW TEMPERATURE PHYSICIST

The University invites applications for a vacancy in the Low Temperature Laboratory. The appointment will be made at the rank and salary appropriate to the training and experience of the applicant. The minimum salaries are $7,000 for Assistant Professor, $9,000 for Associate Professor and $12,000 for the rank of Professor. The laboratory is well equipped. The requirements are for a promising young man to take charge and direct a large part of the work.

For fuller information write to: G. M. Shrum, Head, Department of Physics, University of British Columbia, Vancouver 8, B.C.

UNIVERSITY OF MANCHESTER

Applications are invited from graduates in Physics, Chemistry, Metallurgy, Biology or Engineering for the post of Assistant Lecturer in Dental Materials. The person appointed will be concerned with work on the properties of dental materials. Applications would be considered from persons intending to graduate in 1961. There is wide scope for research in this field and ample facilities are available. Salary on a scale £800 to £950 per annum with membership of F.S.S.U. and Children's Allowance Scheme.

Applications should be sent not later than June 3, 1961, to the Registrar, the University, Manchester 13, from whom further particulars and forms of application may be obtained.

UNIVERSITY OF MANCHESTER

Applications are invited for the post of Assistant Lecturer in Organic Chemistry. Salary on a scale £800 to £950 per annum with membership of the F.S.S.U. and Children's Allowance Scheme.

Applications should be sent not later than June 5, 1961, to the Registrar, the University, Manchester, 13, from whom further particulars and forms of application may be obtained.

UNIVERSITY OF EDINBURGH
DEPARTMENT OF NATURAL PHILOSOPHY

Applications are invited for the posts of Lecturer and Assistant Lecturers in the above Department. Salary scales: Lecturer, £1,050 by £50 to £1,250; Bar £1,300 by £50 to £1,400 by £75 to £1,850 per annum, with placement according to qualifications and experience; Assistant Lecturers, £800 by £50 to £950 per annum. The posts are subject to superannuation, and family allowance is payable where applicable. The successful candidate will be expected to take up duty on October 1, 1961.

Further particulars may be obtained from the undersigned, with whom applications (six copies), giving the names of two referees, should be lodged not later than June 5, 1961.

CHARLES H. STEWART,
Secretary to the University.

UNIVERSITY COLLEGE OF NORTH WALES

Applications are invited for the new position of Head of the Workshop in the Department of Physics. Candidates should have wide experience in precision workshop practice. The workshop is about to be expanded and re-equipped. The salary will be on the Chief Technician scale, which is £895 by £30 to £1,015, the commencing salary being according to qualifications and experience. There is a pension scheme and holidays are generous.

Applications, giving details of age and experience, together with the names of two referees, should be sent by June 1, 1961, to the Professor of Physics, University College of North Wales, Bangor, from whom further information concerning the work may be obtained.

CITY OF LEICESTER EDUCATION COMMITTEE
LEICESTER COLLEGE OF TECHNOLOGY AND COMMERCE

Principal: R. E. Wood, M.Sc., F.Inst.P.

Applications are invited for the post of full-time Assistant Grade B. in the School of Physics and Applied Science. Candidates should be graduates and have had teaching experience. Some experience in industry would be an advantage. Salary: Burnham Scale £700 to £1,150 per annum with increments for graduateship, training and appropriate industrial experience.

Forms of application and further particulars may be obtained from the Registrar, Leicester College of Technology, to whom completed forms should be returned as soon as possible.

UNIVERSITY OF EDINBURGH
BIOPHYSICS DEPARTMENT
RESEARCH ASSISTANTSHIP IN PLANT BIOPHYSICS

Applications are invited from botanists who have recently graduated or who will graduate this summer for a position as Research Assistant to the Head of the Biophysics Department, who is studying the ionic and water relations of plant cells and tissues. The Research Assistant would be expected to attend the department's Postgraduate Course on Biophysics and it would be possible for him or her to register for a Ph.D. The salary offered for a three-year appointment would be £425 by £50 to £525 (including F.S.S.U. benefit); the appropriate starting salary would depend on the amount of postgraduate research experience. The appointment is to start on August 1, 1961, or as soon as possible thereafter.

Applications, giving details of education, etc., should be sent to Dr. J. Dainty, Biophysics Department, West Mains Road, Edinburgh, 9.

SENIOR MAP OFFICERS, DIRECTORATE of Overseas Surveys. Three pensionable posts at Tolworth, Surrey, for men at least 28 on May 1, 1961, to work on land use and forest surveys of overseas territories with the aid of aerial photography; some overseas field work. Qualifications: Degree in a natural science, agriculture, forestry, or geography, and at least five years' practical experience or postgraduate study concerned with overseas land use or forestry projects including use of air photos. Outer London salary ranges from £1,277 to £1,527. Starting pay may be above minimum. Promotion prospects.—Write Civil Service Commission, Burlington Gardens, London, W.1, for application form quoting **5304/61**. Closing date June 21, 1961.

ASSISTANT REQUIRED FOR BIOCHEMICAL research in diseases of the skin. The post which is of technician grade would be suitable for a graduate or a man studying for a science degree in evening classes. Salary, etc., according to the Whitley Council scales and conditions of service. Application to the Secretary, Institute of Dermatology, Lisle St., Leicester Square, W.C.2.

UNIVERSITY OF GLASGOW

LECTURESHIP OR ASSISTANTSHIP IN GEOLOGY

Applications are invited for a Lectureship or an Assistantship in Geology. Salary scale: £1,050 to £1,850 per annum for Lecturers, and £500 to £950 per annum for Assistants. Initial salary according to experience and qualifications. F.S.S.U. and family allowance benefits.

Applications (eight copies for the Lectureship, three copies for the Assistantship) should be lodged, not later than June 10, 1961, with the undersigned, from whom further particulars may be obtained.

ROBT. T. HUTCHESON,
Secretary of University Court.

REPUBLIC OF SUDAN

Applications are invited to fill the post of Veterinary Research Officer (Biochemist) in the Department of Animal Production. Applicants must be Members of the Royal College of Veterinary Surgeons or equivalent. Age limit from 30 to 45 years. Applications will be on contract for five years, with a six month probationary period, and with or without bonus. Salary range with bonus is £S.1,075 to £S.1,675 per annum, and without bonus £S.1,146 to £S.1,786. Starting rate of pay will be fixed in accordance with age, qualifications and experience. A cost of living allowance, which is reviewed every two months, is payable. An outfit allowance of £S.50 is payable when the contract is signed. There is no income tax payable in the Sudan at the present time. Leave accrues at the rate of seven days per month.

Further information and application forms may be obtained from the Appointments Section, Sudan Embassy, 3 Cleveland Row, St. James's, London, S.W.1. Closing date: June 15, 1961.

HERTFORDSHIRE COUNTY COUNCIL

TECHNICAL LIBRARY AND INFORMATION SERVICE

Are you interested in the problems of disseminating information to scientists and technologists? Are you concerned at their ability to use it? If so, there is an opportunity for you to take an active role in improving the situation as a Tutor Librarian at Hatfield College of Technology. Considerable library experience and some lecturing ability essential. For suitably qualified candidates the post is graded on the Burnham Scale for Technical Teachers Grade B, £700 to £1,150 per annum, with additional allowances for degree and Fellowship of the Library Association plus a special responsibility allowance of £120. Duties commence on September 1, 1961.

Full details and application particulars from the Registrar, Hatfield College of Technology, Hatfield, Herts.

CRUMPSALL HOSPITAL

MANCHESTER, 8

Applications are invited for the post of Assistant Biochemist (Basic grade) in the Group Laboratory at Crumpsall Hospital (1,200 beds). Preference will be given to applicants holding the A.R.I.C., the Grad.Mem.R.I.C., or B.Sc. (Hons.) in Chemistry or Biochemistry. Salary range £730 to £1,150, according to qualifications. The post provides an excellent opportunity for a graduate intending to make a career in hospital biochemistry.

Applications, with the names of two referees, should be sent to the Hospital Administrator, Crumpsall Hospital, Manchester.

UNIVERSITY COLLEGE LONDON (GOWER Street, W.C.1) requires Assistant Lecturer or Lecturer in the Department of Mathematics. Preference given to applicants whose interests are in applied mathematics. Duties to commence October 1, 1961. Initial salary within the range £800 to £1,350 per annum, plus £60 per annum London allowance according to qualifications and experience. Superannuation and family allowance.—Applications, to be received by June 10, 1961, should be sent to the Secretary, from whom further particulars may be obtained.

THE GRASSLAND RESEARCH INSTITUTE, Hurley, nr. Maidenhead, requires a person, with training in chemistry or agricultural chemistry, to assist in research studies on the supply of potassium and phosphorus from soils in relation to grassland management. The work will involve development of analytical techniques and field experimentation. The appointment will be in the Assistant Experimental Officer grade, salary £578 at 21, rising to £776 age 26 (maximum at entry) to £957. Minimum qualifications H.N.C. or pass degree.—Apply to Secretary.

DEPARTMENT OF AGRICULTURE

TANGANYIKA

CHEMIST

For research work on coffee; including soil and plant analysis connected with nutritional problems and soil survey work. Candidates (male) must have an honours degree in chemistry or equivalent qualification and not less than two years post-graduate experience or training. Appointment on contract (gratuity terms for one or two tours of 21-27 months with emoluments in scale £1,266 to £2,448. Gratuity 25 per cent of total substantive emoluments. Free passages. Generous leave. Furnished accommodation usually available at low rental. Children's education allowances.

Apply, stating full name and giving brief particulars of qualifications and experience, to Director of Recruitment, Colonial Office, London, S.W.1, quoting BCD.63/8/920/CI.

ST. GEORGE'S HOSPITAL, LINCOLN

DEPARTMENT OF RADIOTHERAPY

Senior Technician or Technician required for the Physics Department. Duties include Physics Workshop, Isotope Laboratory, Radium and Mould Room work. Applicants must have some experience of mould making for X-ray and radium work. Instrument or Physics Workshop experience would be an advantage. In addition to other duties the person appointed will be responsible as a Radium Curator for which he will receive an additional allowance in accordance with the rate laid down. Salary £570 to £710 per annum; senior grade £710 to £905 per annum would be applicable to suitably qualified persons.

Applications, giving full details, including age and experience, together with names of two referees to the Secretary.

UNIVERSITY OF NOTTINGHAM

Applications are invited for an Assistant Lectureship and Lectureship in Physics. Salary scales: Lecturer, £1,050 to £1,850; Assistant Lecturer, £800 to £950, initial salary in each case according to qualifications and experience, with membership of the Universities' Superannuation Scheme and children's allowance.

Conditions of appointment and form of application, which should be returned by June 10, from the Registrar.

UNIVERSITY OF BELFAST

The Senate of the Queen's University of Belfast invites applications for a Lectureship in Civil Engineering from October 1, 1961. Salary range £1,050 to £1,850 plus contributory pension rights under the F.S.S.U. Initial placing on the salary scale will depend on qualifications and experience.

Applications should be received by June 20, 1961. Further particulars may be obtained from G. R. Cowie, M.A., LL.B., J.P., Secretary.

INSTITUTE OF CHILD HEALTH (UNIVERSITY OF LONDON)

Applications are invited for the post of Lecturer in Paediatrics based at the Queen Elizabeth Hospital for Children, Hackney Road, E.2. The successful applicant will be required to undertake clinical work, the co-ordination of postgraduate teaching and clinical or pathological research. Salary will be within the scale £1,350 to £2,200 per annum.

Applications, including the names of three referees, should be addressed to the Secretary, Institute of Child Health, Great Ormond Street, W.C.1, to arrive by June 30, 1961.

APPLICATIONS ARE INVITED FROM A Physicist or Physical Chemist to undertake research in connection with problems in food manufacture. Initial duties will be concerned with investigations into the rate of diffusion of moisture during the drying of confectionery, and the person appointed will be expected to develop experimental techniques appropriate to the study. The candidate must hold a university degree and should have some experience in the conduct of research.—Apply in writing to the Director of Research, British Food Manufacturing Industries Research Association, Randalls Road, Leatherhead, Surrey, giving details of qualifications and salary expected. The post carries comparable pension and life insurance rights. Applications should be marked "Private and Confidential."

RADIATION PHYSICIST: FACULTY APpointment. Teach radiation physics, supervise radiation health programme and conduct own research. Electronic Engineer: Faculty appointment. Conduct own research and consult in biomedical problems, supervise a modern electronics shop.—Professor Charles D. Kochakian, Coordinator Research University of Alabama Medical Center, Birmingham 3, Alabama.

FREETOWN TRAINING COLLEGE FOR TEACHERS

SIERRA LEONE

Applications are invited for the post of Principal. Applicants should possess a good honours degree, a diploma in education and good teaching and Training College experience. Salary £2,250 per annum (consolidated). Plus, in the case of overseas appointee, contract addition of £195 per annum and resettlement grant at the rate of 15 per cent of the aggregate gross salary. Other conditions include (where applicable) free passages on appointment, leave and termination of service, passages for not more than three children and basically furnished accommodation at reasonable rental.

Applications (six copies) giving age, qualifications, and experience, with copies of recent testimonials and the names of three referees, should be sent to the Council for Overseas Colleges of Arts, Science and Technology, 12 Lincoln's Inn Fields, London, W.C.2, from whom further particulars may be obtained. Closing date: June 12, 1961.

UNIVERSITY COLLEGE OF SOUTH WALES AND MONMOUTHSHIRE

CHEMISTRY DEPARTMENT

Applications are invited for the post of Research Assistant in the Department of Chemistry at a salary of £750 per annum. The post is for one year in the first instance and may be renewed up to a total maximum of three years. The successful applicant will be expected to carry out research into the mechanism of polymerization reactions.

Applications, stating age and the names of two referees, should be sent by Saturday, June 3, to the Registrar, from whom further particulars may be obtained.

UNIVERSITY OF NOTTINGHAM

Applications are invited for a Lectureship in Inorganic Chemistry. Initial salary within the scale £1,050 to £1,850 according to qualifications and experience, plus membership of the Universities Superannuation Scheme and children's allowance. Conditions of appointment and form of application, which should be returned by June 10, from the Registrar.

UNIVERSITY OF BRISTOL

Applications are invited for the following appointments in the Department of Geography. (1) Assistant Lectureship tenable from October 1, 1961. Candidates will be preferred who have specialized in Economic Geography and have interests in agricultural or bio-geography. Salary within the scale £800 by £50 to £950 per annum. (2) Demonstratorship, tenable for one year in the first instance, renewable annually up to a maximum of three years. Salary £450 per annum.

Further particulars may be obtained from the Registrar, The University, Bristol, 8, to whom applications should be submitted by May 29, 1961.

ASSISTANT EXPERIMENTAL OFFICERS required by Research Institute (Animal Virus Diseases), Pirbright, Surrey: (1) For Biophysics Department. Work involves application of physical-chemical methods (electron-microscopy, electrophoresis, ultracentrifugation, etc.) to the study of foot-and-mouth disease and other animal virus diseases. Applicants over 22 should have H.N.C. or equivalent. (2) For work connected with production of attenuated strains of foot-and-mouth disease vaccines. Previous experience in virological techniques, preferably including tissue culture, essential. Applicants over 22 should have H.N.C. or F.I.M.L.T., preferably with virology as one subject. Salary dependent on age and qualifications in A.E.O. scale £625 at age 22 rising to £983. Houses available for married applicants. Superannuation scheme.—Applications to Secretary.

GLASSHOUSE CROPS RESEARCH INSTITUTE requires Scientific Officer for plant breeding section, primarily for research on mushroom spawn and breeding for disease resistance in higher plants. Appointment initially in Scientific Officer scale (£717 to £1,222), according to age and experience; superannuation under F.S.S.U. Candidates should have honours degree in appropriate subject, and preferably postgraduate experience in genetics, particularly of micro-organisms, but students with suitable basic training graduating this year may be considered.—Further details available from Secretary to the Institute, Worthing Road, Rustington, Littlehampton, Sussex, to whom applications, with names of three referees, should be submitted before May 31, 1961.

BRADFORD INSTITUTE OF TECHNOLOGY

DEPARTMENT OF MATHEMATICS

Head of Department: J. G. Freeman, M.A., Ph.D.

Applications are invited for the post of: Reader in Numerical Analysis and Director of the Computing Laboratory. Candidates should possess the qualifications and experience to direct research, to direct the work of the Computing Laboratory (which contains both electronic digital and electronic analogue computers), and to take a leading part in advanced teaching. Senior members of staff are encouraged to undertake consultant work in industry and may retain fees paid for such work. The salary attached to the appointment is £1,800 to £2,100 per annum. In the case of a very highly qualified candidate, the Governors may, subject to the approval of the Minister of Education, pay such higher salary above the maximum of the scale as may be considered appropriate. Previous industrial and research experience at a suitable level will be taken into account in fixing the commencing salary.

Further particulars and forms of application may be obtained from the Registrar (Department F), Bradford Institute of Technology, Bradford 7.

HENRY PATTEN,
Clerk to the Governors.

UNIVERSITY OF LIVERPOOL

Applications are invited for the post of Assistant Lecturer or Lecturer in the Department of Geology. The initial salary will be within the range £800 to £1,250, according to qualifications and experience. The post is for a petrologist or mineralogist. Experience of spectroscopic techniques, and possibly also X-ray techniques, is desired. The appointment will commence on October 1, 1961.

Applications, stating age, academic qualifications and experience, together with the names of three referees, should be received not later than June 10, 1961, by the Registrar, from whom further particulars may be obtained.

MACAULAY INSTITUTE FOR SOIL RESEARCH

DEPARTMENT OF MICROBIOLOGY

Applications are invited for the appointment of a Microbiologist with a first- or second-class honours degree in microbiology or bacteriology or botany (with bacteriology) to work on the influence of the root region microflora on the availability of nutrients, particularly phosphorus, to plants. A training in chemistry would be an advantage. The appointment will be made in the Scientific Officer grade, starting salary within the range £738 to £1,222 per annum, according to age, qualifications and experience. Superannuation scheme.

Forms of application may be obtained from the Secretary, The Macaulay Institute for Soil Research, Craigiebuckler, Aberdeen, to whom they should be returned before June 14, 1961.

UNIVERSITY COLLEGE OF SOUTH WALES AND MONMOUTHSHIRE

Applications are invited for the post of Assistant Lecturer or Lecturer in the Department of Mathematics.

Further particulars may be obtained from the Registrar, University College, Cathays Park, Cardiff, to whom applications (six copies) should be sent not later than June 24, 1961.

ST. THOMAS'S HOSPITAL MEDICAL SCHOOL

LONDON, S.E.1

Applications are invited from science graduates for the post of Research Fellow to work in the Department of Bacteriology. A medical qualification is not necessary. Commencing salary within the range £650 to £750, according to age and qualifications, together with children's allowances and superannuation.

Further details may be obtained from the Professor of Bacteriology.

WRIGHT-FLEMING INSTITUTE OF Microbiology, St. Mary's Hospital Medical School, seeks a Medical or Science Graduate with experience of virus isolation and diagnosis for a research project on non-specific urethritis and related problems, to commence in October, 1961. The post would offer an opportunity for work for a higher degree. Salary, etc., according to age and experience.—Apply, with details of career to the Secretary, Wright-Fleming Institute of Microbiology, St. Mary's Hospital Medical School, Paddington, London, W.2, before June 30, 1961.

UNIVERSITY COLLEGE OF SOUTH WALES AND MONMOUTHSHIRE

Applications are invited for a Research Associate to perform theoretical work on semiconductors, as a member of a small group in the Department of Applied Mathematics. The appointment will be for a period of three years in the first place, and will carry a salary of up to £1,000 per annum, depending on age and qualifications.

Applications (including the names of two referees), should reach Professor P. T. Landsberg, Department of Applied Mathematics, University College, Cardiff, Wales, as soon as possible, and not later than June 12, 1961.

MESSRS. CLARKE, CHAPMAN & CO. LTD.

VICTORIA WORKS, GATESHEAD, 8

Invite applicants for the following position: Computer Programmer. The appointed person who must hold a good honours degree in mathematics or theoretical physics, will have considerable freedom for work and will be concerned not only with the mechanics of programming (including passage through an electronic machine) but also with associated preparatory mathematical work. Some time will be available for individual research. Excellent staff conditions and progressive salary commensurate with position and in accordance with age and experience.

Please write in first instance to Personnel Officer at the above address. All applications treated in strictest confidence.

UNIVERSITY OF BIRMINGHAM

DEPARTMENT OF BIOCHEMISTRY

Applications are invited for the post of Research Fellow in the Department of Biochemistry. Stipend, within the range of £800 to £900 per annum, will be related to qualifications and experience. Appointment carries F.S.S.U. and family allowance benefits.

Applications (three copies), naming two referees, should be sent before June 17, 1961, to the Assistant Registrar (Science), the University, Edgbaston, Birmingham, 15, from whom further particulars may be obtained.

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(LIAISON)

A young science graduate, preferably with two or three years experience in industry, is required to develop a new branch of an existing liaison service to the ceramic whiteware industry. Some travelling will be involved. An amiable personality and the capacity to organize are major prerequisites. Appointment will be in the Scientific Officer grade, qualifying for membership of F.S.S.U.

Applications, in writing, to the Director of Research, Dr. N. F. Astbury, The British Ceramic Research Association, Queens Road, Penkhull, Stoke-on-Trent.

UNIVERSITY OF CAMBRIDGE

STATISTICIAN

Applications are invited for the post of Statistician to the Medical School. Applicants should be graduates in mathematics, mathematical statistics, or statistics. Experience with punched cards and electronic computers would be an asset. The appointment will be for five years from October 1, 1961, in the first instance. Salary, £1,250 by £50 to £1,400 by £75 to £1,800, according to experience.

Applications should be made in writing to Dr. G. A. Gresham, the Medical School, Tennis Court Road, Cambridge, not later than June 4, 1961.

INSTITUTE OF CANCER RESEARCH: Royal Cancer Hospital. Research Assistant required in laboratories at Sutton, Surrey, for investigations into the radioactivity of biological material. The post is one of responsibility requiring a variety of experimental skills and personal initiative. Applicants should be over 25 years and possess A.I.S.T., City and Guilds or equivalent qualification, together with experience in a physical or biochemical laboratory. Salary on M.R.C. scales in the range £600 to £750.—Applications, with names of two referees, to the Secretary, 33 Sumner Place, S.W.7, quoting ref.: 301/B/62.

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Further particulars may be obtained from Hospital Secretary, Dudley Road Hospital, Birmingham, 18.

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Further particulars may be obtained from the Registrar, University College of Sussex, Stanmer House, Stanmer, Brighton, to whom applications should be sent by June 8, 1961.

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Assistant Professor in Pharmacology required. Ph.D. or M.B. Salary $6,000 to $8,500, according to qualifications and experience.

Applications to Professor M. F. Murnaghan at the above address.

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One year Visiting Lectureship in Anatomy. To participate in teaching of Gross Anatomy to medical and dental students September, 1961, to June, 1962. Salary: $7,000, plus passage.

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HOUGHTON POULTRY RESEARCH Station invites applications for a Research Worker in its Leucosis Experimental Unit. Veterinary qualification desirable and postgraduate experience in virology, cyto-pathology or allied fields essential. Grading Senior Scientific Officer (£1,302 to £1,654 per annum); commencing salary according to qualifications and experience. Superannuation under F.S.S.U.—Applications, with names of three referees, to the Station Secretary, Houghton, Huntingdon, before June 24, 1961.

HOUGHTON POULTRY RESEARCH Station invites applications for a Physiologist with research experience. Grading Senior Scientific Officer (£1,302 to £1,654 per annum) or Principal Scientific Officer (£1,666 to £2,418 per annum), according to qualifications and experience. Superannuation under F.S.S.U.—Applications, with names of three referees, to the Station Secretary, Houghton, Huntingdon, before June 24, 1961.

HOUGHTON POULTRY RESEARCH Station invites applications for two Research Assistants. Both posts superannuable on the Assistant Experimental Officer grade (£625 to £983 per annum); commencing salary according to qualifications, experience and age. Post (1) Assistant Histologist, main Station. Experience in histological techniques essential. Post (2) Research Assistant in Leucosis Experimental Unit including responsibility for supervision of junior technical staff. Experience in tissue culture techniques desirable.—Applications, with names of three referees, to the Station Secretary, Houghton, Huntingdon, before June 24, 1961.

BIOCHEMISTS: B.SC. OR PH.D. REQUIRED for work on the mechanism of androgen action in protein and nucleic acid synthesis. Opportunity for advancement. Graduate work permitted for B.Sc. appointee.—Professor Charles D. Kochakian, University of Alabama Medical Center, Birmingham 3, Alabama.

BIOCHEMIST, NON-MEDICAL, BASIC grade, required as locum for period July 31 to September 2, 1961, at Group Laboratory, Epsom District Hospital. Salary, etc., as defined by the Whitley Council.—Applications to Group Secretary, Epsom District Hospital, Dorking Road, Epsom, Surrey, by May 31, 1961.

LEVY WEST LABORATORIES OF Wembley require a graduate for work on very pure inorganic chemicals. Some physical leanings useful. Outside experience helpful but not essential. Salary according to qualifications.—Write or telephone WEMbley 1088.

THE LONDON HOSPITAL, WHITECHAPEL, E.1, has vacancy in their Physics Department for a Physicist in the Senior Grade. Applicants should have an honours degree in physics, and previous experience in radiation physics. Duties will include problems arising in radiotherapy, although the department's interests are not limited to this field. There are good opportunities for development and research, and technical assistance including a first-class instrument workshop. Salary £1,300 to £1,750.—Applications, with the names of two referees to the House Governor by May 31.

MEDICAL RESEARCH COUNCIL
NEUROPHARMACOLOGY RESEARCH UNIT
DEPARTMENT OF EXPERIMENTAL PSYCHIATRY, THE MEDICAL SCHOOL, BIRMINGHAM, 15

Applications are invited from graduates and prospective graduates in science to work on a programme of research into the actions of drugs on the central nervous system, using electrophysiological and behavioural techniques. Opportunities for working for a higher degree in the University of Birmingham will be available for those with suitable qualifications.

Applications, in writing, should be addressed to:

Dr. P. B. Bradley,
Neuropharmacology Research Unit,
Department of Experimental Psychiatry,
The Medical School,
Birmingham, 15,

from whom further particulars may be obtained.

UNIVERSITY OF DURHAM
KING'S COLLEGE, NEWCASTLE UPON TYNE, 1

The Council of King's College invite applications for the appointment of two Demonstrators in the Department of Zoology. Both appointments will be for one year in the first instance, renewable annually up to a maximum of three years. The commencing salaries for these posts will be determined at an appropriate point according to age, qualifications and experience on salary scales ranging from £750 to £1,150 per annum, with family allowance and F.S.S.U. benefits.

Further particulars may be obtained from the Registrar and Secretary of King's College, to whom applications, together with the names and addresses of three persons to whom reference may be made, should be addressed so as to reach him not later than June 7, 1961.

UNIVERSITY OF NOTTINGHAM

Applications are invited for a Demonstratorship in Zoology. Salary within the scale £550 by £25 to £600. Applications will be considered from candidates who expect to graduate this year.

Conditions of appointment and form of application, to be returned by June 10, from the Registrar.

HOUGHTON POULTRY RESEARCH Station invites applications for a Biochemist with research experience. Grading Scientific Officer (£717 to £1,222 per annum) or Senior Scientific Officer (£1,302 to £1,654 per annum) according to qualifications and experience. Superannuation under F.S.S.U.—Applications, with names of three referees, to the Station Secretary, Houghton, Huntingdon, before June 24, 1961.

GRANTS & SCHOLARSHIPS

UNIVERSITY COLLEGE OF NORTH STAFFORDSHIRE

Applications invited for Research Studentship in organic chemistry, value £425 per annum (plus fees), provided by Smith, Kline and French Ltd. The successful candidate will work for a higher degree under supervision of Dr. G. Jones, on heterocyclic syntheses in aza-steroid field.

Applications, together with names of two referees, should reach the Registrar, the College, Keele, Staffs, not later than June 17, 1961.

UNIVERSITY COLLEGE OF NORTH STAFFORDSHIRE
DEPARTMENT OF PHYSICS—RESEARCH STUDENTSHIPS AND ASSISTANTSHIPS

A variety of research Studentships and Assistantships are vacant in Physics Department for students completing first degree this Summer. Three main research groups within department with total of 18 postgraduate students at present. Main research interests: (1) Magnetic resonance studies of the solid state including work at very low temperatures; (2) Investigations of gas discharges with particular reference to surface effects. This work is particularly concerned with application of ultra-high vacuum techniques to gas discharges. (3) Studies on strength of glass and similar fibres with particular reference to effect of surface impurities and other defects. Some smaller research groups are studying oxide cathodes and liquid metals at infra-red frequencies.

Further particulars of research studentships available for work in these fields can be obtained from Professor D. J. E. Ingram, Department of Physics, the College, Keele, Staffs.

UNIVERSITY COLLEGE OF NORTH STAFFORDSHIRE
DEPARTMENT OF CHEMISTRY
ALBRIGHT AND WILSON RESEARCH STUDENTSHIP

This Research Studentship, value £425 per annum plus fees for two or three years, is available for thermochemical research on phosphorus compounds, leading to M.Sc. or Ph.D. degree under supervision of Dr. C. T. Mortimer.

Applications from graduates or prospective graduates in chemistry or physics should be sent before July 1, 1961, to the Registrar, the College, Keele, Staffs, from whom further particulars may be obtained.

UNIVERSITY OF MANCHESTER
RESEARCH STUDENTSHIPS IN SCIENCE

Applications are invited for the above studentships, normally tenable for three years and of a value comparable to that of a D.S.I.R. Research Studentship. Candidates must hold the degree of Bachelor or Master of a British University other than Manchester.

Applications should be sent not later than July 1, 1961, to the Registrar, the University, Manchester 13, from whom further particulars and forms of application may be obtained.

GEORGE HENRY LEWES STUDENTSHIP

Applications are invited for the above Studentship which will be vacant on October 1, 1961. The Student is required to give his whole time to research work except such as, in the opinion of the Trustees, does not interfere with his original inquiries.

Candidates should send (a) a statement of their qualifications, and their need of pecuniary help, (b) the subject of their proposed research, (c) the name of one referee, to Professor Sir Bryan Matthews, Physiological Laboratory, Cambridge, by July 1, 1961. The Student is expected normally to work in the Physiological Laboratory, Cambridge, though in exceptional conditions he may obtain permission to work elsewhere. Emolument depends on qualifications, up to a maximum of £750 per annum.

UNIVERSITY COLLEGE OF NORTH STAFFORDSHIRE
DEPARTMENT OF CHEMISTRY
INSTITUTE OF PETROLEUM RESEARCH STUDENTSHIP

This Research Studentship, value £425 per annum plus fees for two or three years, is available for thermochemical research in cyclic hydrocarbons and heterocyclic compounds, leading to M.Sc. or Ph.D. degree under supervision of Dr. C. T. Mortimer.

Applications from graduates or prospective graduates in chemistry or physics, should be sent before July 1, 1961, to the Registrar, the College, Keele, Staffs, from whom further particulars may be obtained.

LECTURES AND COURSES

MIDDLESEX COUNTY COUNCIL EDUCATION COMMITTEE
BRUNEL COLLEGE OF TECHNOLOGY, WOODLANDS AVENUE, ACTON, W.3
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1961/62

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DIFFERENTIAL EQUATIONS
SOLUTION OF PARTIAL DIFFERENTIAL EQUATIONS BY NUMERICAL METHODS
MATHEMATICS FOR MECHANICAL ENGINEERS
MATHEMATICS FOR ELECTRONIC ENGINEERS
INTERMEDIATE STATISTICS
FINAL STATISTICS
QUEUEING THEORY AND APPLICATIONS
INFORMATION THEORY

Full particulars may be obtained from the Head of the Mathematics Department.

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(UNIVERSITY OF LONDON)
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A course of instruction for research workers in Universities and Hospitals will be held in Glasgow from Monday, September 18 to Friday, September 29, 1961. The course will be directed by Dr. J. M. A. Lenihan, Regional Physicist to the Western Regional Hospital Board of Scotland, and Dr. W. Mulligan, Senior Lecturer in Veterinary Biochemistry. The object of the Course is to give instruction in the techniques by which radioactive isotopes are used in medical and biological research. Lectures, demonstrations and laboratory classes will be held in the Glasgow University Veterinary School, the Physics Department of the Western Regional Hospital Board and the Gardiner Institute of Medicine. Twelve places will be available; applicants must be graduates in medicine or in one of the biological sciences. The fee for the Course is twenty guineas.

Application forms and further details may be obtained from the Director of Postgraduate Medical Education, the University, Glasgow, W.2. Application forms should be returned before July 15, 1961. Candidates selected for the Course will be notified shortly after this date.

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SESSION 1961-62

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Applications are invited for enrolment in the above course which will commence in September, 1961. The course is open to graduates and holders of a Diploma in Technology or a suitable H.N.C. or professional accountancy qualification.

Full particulars can be obtained from the Head of the Department of Mathematics at the College, Cathays Park, Cardiff.

ROBERT E. PRESSWOOD,
Clerk to the Governors.

UNIVERSITY OF ABERDEEN

POSTGRADUATE COURSES IN POLYMER CHEMISTRY AND SILICATE CHEMISTRY

Applications are invited for admission to postgraduate courses in Polymer Chemistry and Silicate Chemistry to commence in October, 1961. These courses are intended to lead to the degree of M.Sc., for which the minimum period of study is twelve calendar months. The Department of Scientific and Industrial Research has accepted both courses as suitable for the tenure of its Advanced Course Studentships. Applicants should normally possess, or be about to obtain, a good honours degree: for the course in Polymer Chemistry, in chemistry or physics; for the course in Silicate Chemistry, in chemistry or geology.

Applications for these courses should be submitted not later than Wednesday, May 31, 1961, and addressed to Professor G. M. Burnett, D.Sc., Department of Chemistry, Meston Walk, Old Aberdeen. The names and addresses of two persons who can speak on the applicant's suitability to undertake the course applied for should be given.

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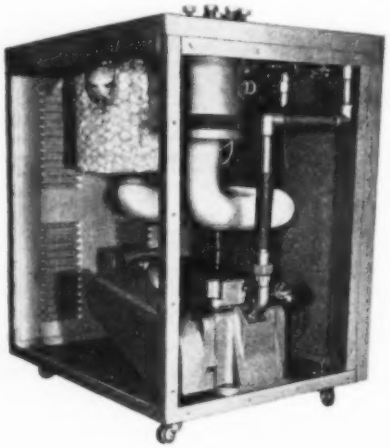

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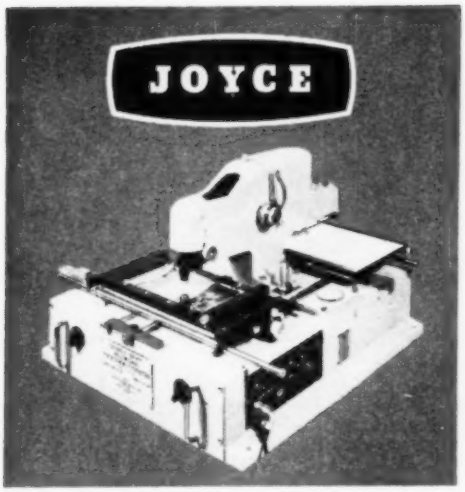

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